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(57) AND PHARMACLUTICAL COMPOSITIONS CONTAINING THILM.

(67) Abstract: Described herrin are compounds having a base structure made up of an altene or an aromatic group to which are hound two tubestituted vicinal amides containing one or more nitmegen amons with hade characteristic and shelr pharmaceutically proceeded by the pharmaceutically among vicinal to the pharmaceutical to th (57) Abstract: Described herein are compounds having a base structure made up of an altene or an aromatic group to which are hound two substituted vicinal amides containing one or more nitrogen atoms with haste characteristic and their pharmaceutically neceptable salts useful for the treatment of diseases that require the use of NK2 anagonists.

WO 02/20437

PCT/EP01/10419

Basic compounds containing tertiary amides with activity on COMPOSITIONS PHARMACEUTICAL AND TACHYKININ RECEPTORS, CONTAINING THEM

Field of the invention

- The present invention relates to compounds having a base structure made up of require the use of NK2 antagonists. The invention further relates to pharmaceutical an alkene or an aromatic group to which are bound two substituted vicinal amides to their tachykinin receptors and, in particular, are useful for the treatment of diseases that 5 containing one or more nitrogen atoms with basic characteristics, and pharmaceutically acceptable salts. Said compounds present activity
 - compositions containing the aforesald products as active principle State of the art 2

In the literature there are known many compounds having activity on tachykinin receptors in general, and as antagonists in particular. In many cases these compounds present structures of a peptide or pseudo-peptide typi

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Amongst tachykinin receptors, the one known as NK2 is widely expressed in the condition in which the release of tachykinins concurs with the genesis of the peripheral nervous system of mammals. One of the various effects produced by Consequently, antagonists of the NK2 receptor can be considered agents capable of controlling the excessive contraction of smooth muscle in any pathological selective stimulation of the NK2 receptor is the contraction of smooth 2

inflammation (including inflammation of a neurogenic origin), pain (including Tachykinins have been implicated in numerous diseases including: asthma, neuropathic, visceral and ocular pain), hemicrania, meumatold arthritis, precough, disease, pulmonary chronic obstructive allergic rhlnitis,

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corresponding disorder.

menstrual tension, emesis (including emesis resistant to ondansetron), oedema, gastric hypermotility, diseases due to oesophageal reflux, Crohn's disease, problems due to gastric evacuation, ulcerous colitis, the frritable-colon syndrome, hypermotility of the detrusor, urinary incontinence, cystitis, and renal colics. 8

In particular, the bronchospastic component of asthma, cough, pulmonary intations, intestinal spasms (for example, in Crohn's disease, in ulcerous colitis or

PCT/EP01/10419

the inftable-colon syndrome), or local spasms of the bladder and of the ureter during cystitis, renal infections and colics can be considered conditions in which the administration of NK2 antagonists may be effective.

Examples of reviews that hypothesize the use of tachykinin antagonists in many of the diseases referred to above are: McLean S. (1996) Med. Res. Rev. 16, 297-317; Holzer P. (1998) Digestion 59(4), 269-83; Maggl C.A. (1997) Pharmacological Research 36(2), 153-69; von Sprecher et al. (1998) Drugs, 1(1), 73-91.

Peptide or pseudopeptides, elther cyclic or linear, are known in the literature for having high antagonistic activity to the NK2 receptor of tachyklnins.

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Also known are many basic compounds containing a substituted aromatic amide and for which there is claimed an activity on the NK1 or NK2 receptor or both, such as those described in EP474561 and WO9410146. The structural characteristics of all these compounds are always considerably different from those that characterize the ones that form the subject of the present invention. Summary of the Invention.

The present invention relates to products having the general formula (I)

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in which the group

is made up of:

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a C₂₋₁₂ alkenyl group or an aromatic group in which the two substituents X and Y are bound to two adjacent carbon atoms;

- X and Y, which are the same as or different from one another, represent a -CO-

or else -SO₂- group;

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- R₁ and R₂, which are the same as or different from one another, represent a -C₂₋₅slkylidene-T-Ar₁ group in which T is a bond or a group chosen from among S,

WO 02/20437

PCT/EP01/10419

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SO or SO2, and Ar₁ is an aromatic group chosen from among benzene, pyridine, pyrimidine, pyrazine, pyridazine, pyriole, furan, thiophene, triazole, imidazole, oxazole, thiazole, isoxazole, naphthalene, quinoline, lsoquinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, isolndole, benzofuran, isobenzofuran, benzothlophene, isobenzothlophene, benzotriazole, benzoimidazole, benzoxazole, benzothlazole, benzoisoxazole, and azulene, possibly substituted with one or two groups chosen from among fluoro-, chloro-, bromo-, nitro-, cyano-, hydroxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, methylamino-dimethylamino-, acetylamino-, tosylamino-, tosylamino-, tosylamino-, carboxy-,

- R₂ and R₄, which are the same as or different from one another, represent a group chosen from among H, -C₁₋₈alkyl, -C₁₋₈alkylidene-NR₆R₆, in which :

carboxyamido-, guanidino-, and sulphamido-;

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R₅ and R₆, which are the same as or different from one another, represent an H, - C₁₋₆alkyl, -C₂₋₄alkylidene-Q group, in which Q is a group chosen from between OR₇ and NR₇R₈ and in which R₇ and R₆, which are the same as or different from one another, represent an H, -C₁₋₆alkyl group; or NR₇R₈ together represent a group chosen from among piperidine, morpholine, pyrrolidine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide piperazine, N-methyl-piperazine,

20 or else NR₅R₆ together represent a group chosen from among:

and aziridine,

a) pyrrolidine, morpholine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, guanidine, guanidine mono-substituted or di-substituted with -C₁₋₃alkyl or -C₁₋₃acyl, -NH-CH=NH groups,

-NH-C(R₁₂)=NH, where R₁₂ is a -C₁₋₆ alkyl group;

25 b) a 4-piperidone ethylene ketal group or else a piperidine of the type

in which R₈ is chosen from among H, -C_{1-s}alkyl, benzyl, OR₁₀, NR₁₀R₁₁, and in which R₁₀ and R₁₁, which are the same as or different from one another, represent an H, -C_{1-s}alkyl group, or else NR₁₀R₁₁ together represent a group chosen from among piperidine, morpholine, pyrrolidine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, piperazine, *N*-methyl-piperazine, and aziridine;

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WO 02/20437 PCT/RP01/10419

c) a piperazine of the type

in which E represents a bond or else a group chosen from among -CO-, -SO $_{z^{\star}}$,

-SO₂NH- and R₁₃ is a group chosen from among H, - C₁₋₃ alkyl, -(CH₂)_h-adamantyl, -(CH₂)_h- Ar₂ in which n = 0,1,2 and Ar₂ is an aromatic group chosen from between naphthalene and benzene possibly substituted with 1, 2, 3 groups chosen from among F, Cl, CF₃, OH, OCH₃, SOCH₃, COF₅, CN, C₁₋₃alkyl;

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with the limitation that at least one between R2 and R4 must always be a

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-Cr.salkylidene-NRsRs group, as defined above, understood both as individual stereoisomers, including those due to atropolsomery, and as mixtures in the racemic or non-racemic form, and their pharmaceutically acceptable salts.

Detailed description of the Invention

The present invention enables the aforesald problems to be overcome thanks to products of formula (1), as previously defined.

Preferably according to the invention the group



is made up of:

a) an olefin chosen from among:

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in which Z and W, which are the same as or different from one another, represent an H, $C_{1.5}$ alkyl group, or else together represent a $C_{2.6}$ alkylidene group;

b) an aromatic group Ar, either mono-cyclic or bl-cyclic, in which the substituents X and Y are in an ortho position with respect to one another, the said group being chosen in the group made up of: benzene, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, furan, thiophene, triazole, imidazole, oxazole, thiazole,

WO 02/20437 PCT/EP01/10419

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isoxazole, naphthalene, quinoline, Isoquinoline, quinazoline, quinoxaline, clinoline, phthalazine, Indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, benzotriazole, benzothiazole, and benzolsoxazole,

- s said aromatic group being possibly further substituted with one, two, three or four groups, which are the same as or different from one another, chosen in the group made up of: fluoro-, chloro-, bromo-, nitro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, methylamino-, acetylamino-, mesylamino-, tosylamino-, tosylamino-, carboxy-, carboxyamido-, o guanidino-, and sulphamido-;
 - and the other substituents are as previously defined.

A selection of preferred compounds, having the general formula (I), are those in

- R₁ and R₃, which are the same as or different from one another, represent a -C₂.
 salkylidene-T-Ar₁ group in which T is a bond or a group chosen from between S and SO, and Ar₁ is an aromatic group chosen from among benzene, naphthalene, quinoline, Isoquinoline, quinozoline, quinoxaline, cinnoline, phthalazine, indole, isoindole, benzofuran, isobenzofuran, benzothlophene, isobenzothlophene, benzotriazole, benzolmidazole, benzoxazole, benzothlazole, and benzotsoxazole.
 - possibly substituted with one or two groups chosen from among fluoro-, chloro-, cyano-, hydroxy-, methoxy-, trifluoromethyk-, trifluoromethoxy-, amino-, acetylamino-, mesylamino-, tosylamino-, tosylam
- R₂ and R₄, which are the same as or different from one another, represent a group chosen from among H, -C₁₋₆alkyl, -C₁₋₆alkylldene-NR₆R₆ in which :
- C₁₋₅alkyl, -C₂₋₅alkylidene-Q group, in which Q is a group chosen from between OR₇ and NR₇R₈ and in which R₇ and R₈, which are the same as or different from one another, represent an H, -C₁₋₅alkyl group; or NR₇R₈ together represent a group chosen from among piperidine, morpholine, pyrrolidine, thiomorpholine, thiomorpholine, and N-methyl-
- piperazine, or else NR₆R₈ together represent a group chosen from among:

WO 02/20437 PCT/RP01/10419

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a) pyrrolidine, morpholine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, guanidine, guanidine mono-substituted or d- substituted with -C₁-salkyl or -C_{1-s}acyl, -NH-CH=NH,

-NH-C(R₁₂)=NH groups, where R₁₂ is a -C₁₋₅ alkyl group;

b) a 4-plperidone ethylene ketal group or else a piperidine of the type

In which R₉ is chosen from among H, -C_{1-s}alkyl, benzyl, OR₁₀, and NR₁₀R₁₁, and in which R₁₀ and R₁₁, which are the same as or different from one another, represent an H, -C_{1-s}alkyl group, or else NR₁₀R₁₁ together represent a group chosen from among piperidine, morpholline, pyrrolldine, thlomorpholline, thlomorphollin-1-oxide, thlomorphollin-1,1-dioxide, piperazine, N-methyl-piperazine, and azlridine;

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c) a piperazine of the type

in which E represents a bond or else a group chosen from among -CO-, -SO₂-, -CONH-, -SO₂NH-, and R₁₃ is a group chosen from among H, - C_{1.5} alkyl, -(CH₂)-

15 -CONH-, -SO₂NH-, and R₁₉ is a group chosen from among H₁ - C₁₋₅ alkyl, -(CH₂)_n- adamantyl, -(CH₂)_n- A₁₂ In which n = 0.1,2 and A₁₂ is an aromatic group chosen from between naphthalene and benzene possibly substituted with 1, 2, 3 groups chosen from among F, CI, CF₃, OH, OCH₃, SOCH₃, OCF₃, CN, and C₁₋₆alkyl; with the limitation that at least one between R₂ and R₂ must always be a -C₂.

with the limitation that at least one between R₂ and R₄ must always be a -C₁.

salkylidene-NR₅R₆ group as defined above, and the other substituents are as defined above.

A first particular selection of further preferred compounds are those of the general formula (I) in which the group:



25 may be an olefin chosen from between

WO 02/20437

PCT/EP01/10419

X

In which Z and W, which are the same as or different from one another, represent an H, $C_{1.6}$ alkylidene, and the other

substituents have the meanings previously defined.

- To be considered as preferred compounds of the present solution are those in which the -C₂₄elkylldene part of Z and W is chosen from among -(CH₂)x-, -(CH₂)x-, -(CH₂)x-; the -C₂₋₅elkylldene part of R₁ and R₃ is chosen among -(CH₂)x-, -(CH₂)x-, -(CH₂)x-, isopropylldene, isobutylldene; the -C₁₋₂elkylldene part in R₂ and R₄ is chosen from among -CH₂-, -(CH₂)x-, -(CH₂)x-, -(CH₂)x-, isopropylldene;
- •Ct.salkyl is chosen from among methyl, ethyl, propyl, isopropyl, butyl, ter-butyl; and -Ct.sacyl is chosen from among formyl, acetyl, propanoyl, and isopropanoyl. Particularly preferred are to be considered the compounds in which:
- Z and W, which are the same as or different from one another, are H or methyl or together represent a butylidene group, and X and Y represent a -CO- group.
- According to this first selection, as defined above, the following compounds are absolutely preferred:
 -c/s-but-2-enedioic acid bis-[[2-(3,4-dtchloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide], and
- cyclohex-1-ene-1,2-dicarboxyllc acid bis-[[2-(1H-Indol-3-yl)-ethyl]-(2-morpholin-4-yl-ethyl)-amide].
- A second particular selection of preferred compounds is represented by those of the general formula (I), in which the group:



is an aromatic group Ar, either mono-cyclic or bi-cyclic, with the substituents X and Y in an ortho position with respect to one another,

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chosen from among benzene, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, furan, thiophene, triazole, imidazole, oxazole, thiazole, isoxazole, naphthalene, quinolline, isoquinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, isolndole, benzofuran, isobenzofuran, benzothlophene, isobenzothlophene,

WO 02/20437 PCT/EP01/10419

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benzotriazole, benzoimidazole, benzoxazole, benzotriazole, and benzoisoxazole, possibly further substituted with one, two, three or four groups, which are the same as or different from one another, chosen from among fluoro-, chloro-, bromo-, nitro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethyl-, trifluoromethoxy-, amino-, methylamino-, dimethylamino-, acetylamino-, mesylamino-, tosylamino-, tosylamino-, tosyloxy-, carboxy-, carboxyamido-, guanidino-, and sulphamido-, and the other substituents are as previously defined.

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To be considered as particularly preferred compounds are compounds in which :

- the aromatic group Ar is chosen in the group made up of: benzene, pyridine, pyrazine, pyrimidine, naphthalene, quinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, benzofuran, benzothlophene, benzothlazole, and benzolsoxazole, and is possibly further substituted with one, two, three or four groups, which are the same as or different from one another, chosen from among: fluoro-, chloro-, nitro-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, and guanidino.

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To be considered as even more preferred are those in which:

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 the aromatic group Ar is chosen in the group made up of benzene, naphthalene, pyrazine, and pyridine possibly further substituted with one, two, three or four groups, which are the same as or different from one another, chosen from among: fluoro-, chloro-, nitro-, amino-, hydroxy-, mesylamino-, and tosyloxy-;

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- R₁ and R₃, which are the same as or different from one another, represent a
 -C₂₋₆alkylidene-T-Ar₁ group in which T is a bond or a group chosen from between
 S and SO, and Ar₁ is an aromatic group chosen from among benzene,
 naphthalene, quinoline, indole, benzofuran, benzothlophene, benzoxazole, and
 benzothlazole, possibly substituted with one or two groups chosen from among
 fluoro-, chloro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-,
 trifluoromethoxy-, amilno-, acetylamino-, mesylamino-, and guanidino-;
- R₂ and R₄, which are the same as or different from one another, represent a group chosen from among H, -C₁₋₆alkylidene-NR₆R₆ in which:
 - 30 R₅ and R₆, which are the same as or different from one another, represent an H, -C_{1.5}alkyl, -C_{2.5}alkylidene-Q group in which Q is an OR₇ group and In which R₇ represents an H, -C_{1.5}alkyl group,

WO 02/20437 PCT/EP01/10419

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or else NR_sR_s together represent a group chosen from among:

- a) pyrrolidine, morpholine, thiomorpholine, thlomorpholin-1-oxide, thlomorpholin-1,1-dioxide, guanidine, guanidine mono-substituted or di-substituted with -C₁₋₈alkyl or -C₁₋₈acyl, -NH-CH=NH,
- -NH-C(R₁₂)=NH groups, where R₁₂ is a -C₁₋₅ alkyl group;
- b) a 4-piperidon ethylene ketal group or else a piperidine of the type



in which R₉ is chosen from among H, OH, piperidine, morpholine, thlomorpholine, thlomorpholine, thlomorpholin-1-oxide, thlomorpholin-1, -dioxide;

10 c) a piperazine of the type

In which E represents a bond or else a group chosen from between -CO- and - CONH-, and R₁₃ is a group chosen from among H, - C₁₋₆ alkyl, -(CH₂)_n-adamantyl, - (CH₂)_n- Ar₂ in which n = 0,1,2 and A₇ is a benzene possibly substituted with 1, 2, 3

- groups chosen from among F, Ci, CF₃, OH, OCH₃, SOCH₃, OCF₃, CN, C₁₋₆alkyl the -C₂₋₆alkylidene part of R₁ and R₃ is chosen in the -(CH₂)₂-, -(CH₂)₃-, -(CH₂)₄-, Isopropylidene, Isobutylidene group; the -C₁₋₆alkylidene part in R₂ and R₄ is chosen from among -CH₂-, -(CH₂)₂-, -(CH₂)₄-, Isopropylidene; -C₁₋₆alkyl is chosen from among methyl, ethyl, Isopropyl, butyl, ter-butyl; and -C₁₋₆acyl is
 - chosen from among formyl, acetyl, propanoyl, isopropanoyl.

 Finally, as absolutely preferred compounds, according to this second selection as defined above, the following compounds are to be considered:

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N.N-bls-{2-(1H-Indol-3-yl)-ethyl]-N-methyl-N-{2-[4-(3-nitro-phenylcarbamoyl)-piperazin-1-yl]-ethyl}-pthalamide;

N-(2-[4-(2-tert-butyl-phenylcarbamoyl)-piperazin-1-yl]-ethyl}-N,N-bis-[2-(1H-Indol-3-yl)-ethyl]-N-methyl-phthalamide;

N-[2-(4-benzyl-piperazin-1-yl)-ethyl]-N,N-bis-[2-(1H-indol-3-yl)-ethyl]-N-methyl-phthalamide;

N-[2-(4-benzylcarbamoyl-piperazin-1-yl)-ethyl]-N,N-bis-{2-(1H-indol-3-yl)-ethyl]-N-

PCT/EP01/10419

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N-[2-(4-benzyl-piperazin-1-yi)-ethyi]-N-[2-(1H-Indol-3-yi)-ethyi]-N-(2-morpholin-4yl-ethyi]-N-(2-naphthalene-2-yl-ethyi)-phthalamide;

N-[3-(4-benzyl-piperazin-1-yl)-propyl]-N,N-bis-[2-(1H-Indol-3-yl)-ethyl]-N-methyl-

N.N-bis-[2-(1H-indol-3-yl)-ethyl]-N-methyl-N-2-[4-(4-trifluoromethoxy-

phenylcarbamoyl)-piperazin-1-yl]-ethyl}-phthalamide;

N,N-b/s-{2-(1H-indol-3-yl)-ethyl]-N-methyl-N-[2-(4-phenylcarbamoyl-piperazin-1-

yl}-ethyl]-phthalamide;

10 N-{2-[4-{3,4-dichloro-phenylcarbamoyl}-piperazin-1-yi]-ethyl]-N,N-bis-[2-{1H-indol-3-yl}-ethyl]-N-methyl-phthalamide;

cis-but-2-enedlolc acid bis-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-ylpropyl)-amide] Naphthalene-2,3-dicarboxylic acid bis-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholln-4-yl-15 ethyl)-ethyl]-(2-morpholln-4-yl-

Naphthalene-2,3-dicarboxylic acid *bis*-[[2-(5-fluoro-1H-Indol-3-yl)-ethyfl_(3-morpholin-4-yl-propyl)-amide];

Cyclohex-1-ene-1,2-dicarboxylic acld bis-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholin-4-yl-ethyl)-amide]

20 Pyrazin-2,3-dicarboxyllc acid 2-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide] 3-[[2-(1H-Indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-amide];

Pyrazin-2,3-dicarboxylic acid 2-[[2-(3,4-dichloro-phenyl)-ethylj-(3-morpholin-4-yl-propyl)-amide] 3-([2-(1H-indol-3-yl)-ethyl)-amide);

N', N²-bis-{2-(1H-indol-3-yl)-ethyl]-N', N²-bis-{3-morpholin-4-yl-propyl)-4-nitro-

25 phthalamide;

Naphthalene-1,2-dicarboxylic acid bis-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yt-propyl)-amide];

N', N²-bis-{2-(1H-indol-3-yl)-ethyl N', N²-bis-(2-morpholin-4-yl-ethyl)-4-nitro-

phthalamide;

30 N', N^2 -bis-{2-(1H-Indol-3-yl)-ethyl]-N', N^2 -bis-(3-morpholin-4-yl-propyl)-3-nitrophthalamide;

N¹,N²-bis-{2-(3,4-dichloro-phenyl)-ethyl]-4-hydroxy-N¹,N²-bis-(3-morpholin-4-yl-

WO 02/20437

PCT/EP01/10419

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propyl)-phthalamide;

4-Hydroxy-*N', N²-bis-*[2-(1H-indol-3-y/)-ethy/]-*N', N²-bis-*(3-morpholin-4-y/-propy/)phthalamide;

N', N²-bis-[2-(3,4-dichloro-phenyl)-ethyl]-N', N²-bis-(3-morpholin-4-yl-propyl)-4-

nitro-phthalamide;

Pyridin-3,4-dicarboxylic acid b/s-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-ylpropyl}-amide];

 $4-amino-N',N^2-bis-\{2-(1H-indol-3-yl)-ethylj-N',N^2-bis-(3-morpholin-4-yl-propyl)-phthjalamide;$

10 N', N²-b/s-{2-(1H-indol-3-yl)-ethyl}-4-methanesulphonylamino-N', N²-bis-{3-morpholin-4-yl-propyl}-phthalamide;

Toluene-4-sulphonic acid 3,4-bis-[[2-(1H-Indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-carbamoyl]-phenyl ester;

benzene-1,2-disulphonic acid bis-[[2-(1H-indol-3-yl)-ethyl]-(3-morpholin-4-yl-

propyt)-amide];

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Benzene-1,2-disulphonic acid bis-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholin-4-yl-ethyl)-

N.N*-bis-[2-(1H-indol-3-yi)-ethyl N,N*-bis-(3-morpholin-4-yl-propyl)-phthalamide; N.N*-bis-[2-(3,4-djchloro-phenyl)-ethyl

phthalamide;

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N-{2-(1H-Indol-3-yl)-ethyl]-N-methyl-N'-(2-morpholin-4-yl-ethyl)-N'-(2-naphthalene-2-yl-ethyl)-phthalamide;

N.N-bis-{2-(3,4-dichloro-phenyl)-ethylj-N,N-bis-(2-morpholin-4-yl-ethyl)-phthalamide;

25 N.N-bis-{2-(1H-Indol-3-yl)-ethyl]-N-methyl-N-(3-thiomorpholin-4-yl-propyl)-phthalamide;

N,N-b/s-[2-(1H-Indol-3-y/)-ethy/]-N,N-b/s-(3-thlomorpholin-4-y/-propy/)-phthalamide;

N-(2-(1,4]bipiperidinyl-1'-yl-ethyl)-N,N-bis-[2-(1H-Indol-3-yl)-ethyl]-N-methyl

30 phthalamide;

N.N-bis-(3-[1,4]bipipendinyl-1'-yl-propyl)-N,N-bis-(2-(1H-Indol-3-yl)-ethyl)phthalamide;

•

PCT/EP01/10419

12

N,N-bis-{2-morpholin-4-yl-ethyl N,N-bis-(2-naphthalene-2-yl-ethyl)-phthalamide; N,N-bis-{2-(1H-indol-3-yl)-ethyl N,N-bis-(2-morpholin-4-yl-ethyl)-phthalamide; N,V-bis-{2-(1H-indol-3-yl)-ethyl]-N,N-bis-(2-morpholin-4-yl-ethyl)-N-{2-naphthalene-2-yl-ethyl-naphthalamide:

s N,N-b/s-[2-(5-fluoro-1H-Indol-3-yl)-ethyl]-N,N-b/s-(3-morpholin-4-yl-propyl)phthalamide;

 $N_iN-bis-\{2-(1H-IndoI-3-yi)-ethyl]-N-methyl-N-(3-morpholin-4-yl-propyi)-phihalamide; \\$

N.N-bis-{2-{bis-{2-{bis-{2-methoxy-ethyl}-aminoj-ethyl}- N.N-bis-{2-{1H-indol-3-yl}-ethyl}- 10 phthalamide;

N-{2-{4-{N-{2-tert-butyl-phenyl}-carbamimidoyi]-piperazin-1-yl}-ethyl}-N,N-b/s-{2-(1H-indol-3-yl)-ethyl}-N-methyl-phthalamide;

N-(2-(4-[N-(2-tert-butyl-phenyl)-N-methyl-carbamimidoyl]-piperazin-1-yl}-ethyl)-N,N-bis-(2-(1H-Indol-3-yl)-ethyl]-N-methyl-phthalamide; N-{2-{4-{N-{2-4ert-butyl-phenyl}-N-methyl-carbamimidoyl]-piperazin-1-yl}-ethyl}-N-[2-{3,4-dichloro-phenyl}-ethyl]-N-[2-{1H-indol-3-yl}-ethyl]-N-methyl-phthalamide; N-{2-{3,4-dichloro-phenyl}-ethyl]-N-{2-{1H-indol-3-yl}-ethyl]-N-methyl-N-{2-{4phenylacetyl-piperazin-1-yl}-ethyl]-phthalamide;

22

N,N-b/s-{2-(1H-indot-3-yl)-ethyl}-N-methyl-N-(2-[4-(tricyclo[3.3.1.109]decane-1-

20 carbonyl)-piperazin-1-yi]-ethyl)-phthalamide;

N.N-bis-{2-(1H-indot-3-yl)-ethyl]-N-methyl-N-{2-[4-(tricyclo[3.3.1.1^{0.0}]-dec-1-yt-acetyl)-piperazin-1-yl]-ethyl}-phthalamide;

N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-N,N-bis-[2-(1H-indol-3-yl)-ethyl]-N-methyl-phthalamide; N,N-bis-[2-(1,4-dioxa-8-aza-spiro[4,5]dec-8-yl)-ethyl]-N,N-bis-[2-(1H-indol-3-yl)-

25 N,N-bis-{2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl}-ethyl]-N,N-bis-{2-(1H-Indot-3-yl}-ethyl]-phthalamide;
N-{2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl}-ethyl]-N,N-bis-{2-(1H-Indot-3-yl}-ethyl]-N-

methyl-phthalamide. N-{2-[4-(Butane-1-sulfonyl)-piperazIn-1-yl]-ethyl}-N,N-bis-[2-(1*H*-Indol-3-yl)-ethyl]-

/k-[2-(4-Allylcarbamoyl-piperazin-1-yl)-ethyl]-N,N-bis-[2-(1*H-*Indol-3-yl)-ethyl]-N

N-methyl-phthalamide

2

methyl-phthalamide

WO 02/20437

PCT/EP01/10419

13

N,N-Bis-[2-(1*H-*Indol-3-yl)-ethyl]-N-methyl-N-[2-(4-thiomorpholin-4-yl-methylpiperidin-1-yl)-ethyl]-phthalamide N,N-Bis-[2-(1*H*-Indol-3-yi)-ethyl]-N-methyl-N-{2-[4-(4-nitro-benzenesulfonyl)-piperazin-1-yi]-ethyl]-phthalamide

N,N-Bis-[2-(1H-indol-3-yl)-ethyl]-N-methyl-N-[2-(4-phenylmethanesulfonyl-piperazin-1-yl)-ethyl]-phthalamide

 $\label{eq:NN-Bis-2-4} N.N-Bis-[2-(1/E) - (1/E) - (1/$

3-{4-{2-[[2-(H-Indol-3-yl}-ethyl]-(2-([2-(H-Indol-3-yl)-ethyl]-methyl-carbamoyl)-10 benzoyl)-amino]-ethyl}-piperazine-1-sulfonyl)-thiophene-2-carboxylic acid methyl

piperazin-1-yl]-ethyi}-phthalamide

N.N-Bis-[2-(1*H*-indol-3-yl)-ethyl]-N-methyl-*N*-{2-{4-(2-nitro-benzenesulfonyl)pineszyn 1-yll othyl otthelenide

15 piperazin-1-yi]-ethyi}-phthalamide

N-{2-[4-(Benzo[6]thiophene-2-carbonyl)-piperazin-1-yi]-ethyl}-N,N-bis-[2-(1*H*-Indol-3-yl)-ethyl]-N-methyl-phthalamide

N-{2-[4-(3,5-Dimethyl-isoxazole-4-sulfonyl)-piperazin-1-ylj-ethyl}-N,N-bis-[2-(1*H*-indol-3-yl)-ethyl]-N,-methyl-phthalamide

20 N-{2-{4-{N-(2-4ert-Butyt-phenyt)-N--furan-2-ylmethyt-carbamhridoyl]-piperazin-1-yl)-ethyl)-N,N-bls-{2-{4-{1M-indol-3-yl}-ethyl}-N--methyl-pthalamide, acetic acid salt N-{2-{4-{N-bls-2-ylmethyt-N-{2-methyl-pthalamyt-ethyl}-carbamimidoyl]-piperazin-1-yl}-ethyl)-N,N-bls-{2-{1M-indol-3-yl}-ethyl}-N-methyl-phthalamide, acetic acid salt N-{2-Benzyl-piperazin-1-yl}-ethyl}-N-{2-{4-benzyl-piperazin-1-yl}-N-{2-{4-benzyl-piperazin-1-yl}-N-

25 indol-3-yl)-ethylj-N-methyl-phthalamide

N-{2-(4-Benzyl-piperazln-1-yl)-ethyl]-N-{2-(1H-Indol-3-yl)-ethyl]-N-methyl-N-{2-(4-nitro-phenyl)-ethyl]-phthalamide

N-[2-(4-Benzyt-piperazin-1-yl)-ethyl]-N-(2-biphenyt-4-yl-ethyl)-N-[2-(1*H-*Indot-3-yl)ethyl]-N-methyl-phthalamide 30 According to the present invention the pharmaceutically acceptable salts of the compounds of the general formula (I) are those formed therefrom with organic and Inorganic acids chosen from the following group: hydrochloric acid, hydrobromic

PCT/EP01/10419

7

acid, sulphuric acid, phosphoric acid, carbonic acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, oxalic acid, malonic acid, malic acid, succinic acid, tartaric acid, citric acid, methanesulphonic acid, p-toluenesulphonic acid, maleic acid, and fumaric acid.

- s As may be seen from the formula and from the examples given above, the compounds that form the subject of the present invention are characterized in that they present a base structure made up of an olefin or of an aromatic group, to which are bound two substituted vicinal amides, preferably tertiary, each of which carries another aromatic group and, at least one of which carries one or more to basic nitrogens.
- It may moreover be noted that the compounds according to the invention present substantially simple structures; that preferably their molecular weight is less than 1000; and that they present, at the most, two stereogenic centres.
- The compounds forming the subject of the present invention have proved active on tachykinin receptors, and consequently a use thereof is contemplated in pharmaceutical formulations for the treatment of diseases in which tachykinins are implicated.
- These compounds are therefore viewed as valid alternatives to known compounds active on tachykinin receptors, and In particular on NK2 antagonists.
- The compounds forming the subject of the present invention can be obtained by means of reactions of condensation between the pre-formed amines and the corresponding di-acids (or synthetic equivalent), using reagents and adopting experimental conditions as reported in the current specific literature and consequently well known to a person skilled in the art, for example according to the reaction schemes illustrated hereinafter by way of example as Procedure A
- Non-limiting examples of the present invention are the compounds described

and Procedure B.

The compounds were characterized using magnetic resonance techniques (data acquired at the temperature of 300°K, at 500 MHz in DMSO-d6) and mass spectrometry (with the ESI technique).

EXAMPLES

WO 02/20437

23

PCT/EP01/10419

Procedure A (from anhydrides)

appropriate secondary amine B (1.0 mmol) were added to a solution of an appropriate secondary amine B (1.0 mmol) in 30 ml of N,N-dimethylformamide. After stirring for 10 minutes, the following were added to the solution, in succession: 470 mg of bromotripyrrolidinephosphonium hexafluorophosphate (1.0 mmol), 1 mmol of an appropriate amine B1, and at least 2 mmol of triethylamine. After 12 hours of stirring at room temperature, followed by aqueous work-up, the residue deriving from the organic phase was purified by chromatography.

10 Example 1 - N.N-bis-R-(1H-indol-3-vl)-ethyfl-N-methyr-N-/2-14-(3-nltro-phenylcarbamoyl)-piperazin-1-vl]-ethyll-phthalamide

(A = benzene, X = Y= CO, R_1 = R_3 = 2-(1H-indol-3-yl)-ethyl, R_2 = methyl, R_4 = 2-[4-(3-nitro-phenylcarbamoyl)-plperazin-1-yl]-ethyl)

1H-NIMR; c.s.(ppm); 2.15(m); 2.20(m); 2.39(t); 2.45(m); 2.58(t); 2.78(s); 2.83(s); 2.90-3.02(m); 3.00(s); 3.02(s); 3.20(t); 3.34-3.69(m); 6.80(m); 6.90-7.09(m); 7.15(d); 7.22(m); 7.27-7.53(m); 7.77(m); 7.88(m); 8.44-8.48(m); 8.93-8.99(m); 10.74-10.83(m).

MS; m/z = 741 (MH⁺).

Example 2 - N-(2-14-(2-1ert-butyt-phenylcarbamoyl)-piperazin-1-vII-ethyl)-N,N-bis-

20 [2-(1H-indol-3-vl)-ethyll-N-methyl-ohthalamide

(A = benzene, X = Y= CO, R₁= R₃= 2-(1H-Indol-3-yl)-ethyl, R₂= methyl, R₄ = 2-(4-(2-tert-butyl-phenylcarbamoyl)-piparazin-1-yl]-ethyl)

1H-NMR; c.s.(ppm): 1.27-1.39(m); 2.13(m); 2.38(t); 2.42-2.47(m); 2.77(s); 2.83(s); 2.91-3.02(m); 3.00(s); 3.03(s); 3.39-3.45(m); 3.58-3.70(m); 6.80(m); 6.86-7.09(m);

25 7.16(m); 7.22(m); 7.26-7.48(m); 7.62(dd); 7.77-7.84(m); 10.74-10.84(m). MS; m/z = 752 (MH⁺). Example 3 - N-I2-(4-benzyl-piperazin-1-yl)-ethyll-N.N-bis-I2-(1H-indol-3-yl)-ethyll-N-methyl-phthalamide (R₄ = 2-(4-benzyl-piperazin-1-yl]-ethyl, and the other substituents as in Example 1) 10. 14-NMR; c.s.(ppm): 2.11-2.46(m); 2.76(s); 2.82(s); 2.88-3.00(m); 2.98(s); 3.01(s); 3.19(t); 3.19(t); 3.38(m); 3.44(s); 3.53(b); 3.60-3.68(m); 6.78(m); 6.88-7.08(m); 7.12(d); 7.18-7.46(m); 7.59(d); 7.61(d); 7.081(m).

PCT/EP01/10419

16

 $MS; m/z = 667 (MH^*).$

Example 4 - N-[2-(4-benzylcarbamoyl-piperazin-1-yl)-ethyll-N/N-bls-[2-(1H-indol-3-

vl)-ethyll-N-methy-phthalamide

 $(R_4$ = 2-(4-benzylcarbamoyl -piperazin-1-yl)-ethyl, and the other substituents as in Example 1)

1H-NMR; c.s.(ppm): 2.07(m); 2.12(m); 2.34-2.43(m); 2.47(m); 2.54m); 2.76(s); 2.82(s); 2.90-3.01(m); 2.99(s); 3.02(s); 3.16-3.24(m); 3.39(m); 3.54-3.69(m); 4.21(m); 6.79(m); 6.89-7.08(m); 7.13(d); 7.18-7.47(m); 7.61(m); 10.73-10.83(m).

10 Example 5 - A-I2-(4-benzyl-piperazin-1-yl)-ethyll-N-I2-(1H-indol-3-yl)-ethyll-N-I2morpholin-4-yl-ethyl)-N-(2-naphthalene-2-yl-ethyl)-phthalamide

MS; m/z = 710 (MH⁺).

 $(R_2=2-(4-benzyl-piperazin-1-yl)-ethyl, R_3=2-naphthaiene-2-yl-ethyl, R_4=2-morpholin-4-yl-ethyl, and the other substituents as in Example 1)$

1H-NMR; c.s.(ppm): 2.15-4.28(b); 6.75-6.83(m); 6.87-6.94(m); 6.97-7.10(m); 7.13(d); 7.22(b); 7.28-7.53(m); 7.61(d); 7.64(d); 7.74-7.90(m); 9.76(b); 10.77(b);

15 7.13(d); 7.22(b); 7.28-7.53(m); 7.61(d); 7.64(d); 7.74-7.90(m); 9.76(b) 10.80(b); 10.85(b).

 $MS; m/z = 777 (MH^*).$

Example 6 - A-13-(4-benzyl-piperazin-1-yl)-propyil-N,N-bis-(2-(1H-Indol-3-yl)-

ethyll-N-methyl-phthalamide

20 (R₄ = 3-[4-benzyl-piperazin-1-yi]-propyl, and the other substituents as in Example 1) 1H-NMR; c.s.(ppm); 1.57-1.76(m); 2.01-2.38(m); 2.76(s); 2.81-2.99(m); 2.82(s); 2.97(s); 3.00(s); 3.35(s); 3.44(s); 3.59-3.68(m); 6.79(m); 6.88-7.08(m,6H); 7.14-7.46(m,12H); 7.59(m,1H); 10.74-10.82(m,2H).

25 MS; m/z = 681 (MH⁺).

Example 7 - M.N-bis-12-(1H-Indol-3-vI)-ethvil-M-methyl-N-2-[4-(4-trifluoromethoxy-

phenylcarbamoyl)-piperazin-1-yll-ethyl)-phthalamide

 $(R_4=2-[4-(4-trifluoromethoxy-phenylcarbamoyl)-piperazin-1-yl]-ethyl, and the other substituents as in Example 1)$

30 1H-NMR; c.s.(ppm); 2.13(m); 2.38(t); 2.45(m); 2.57(t); 2.77(s); 2.83(s); 2.90-3.03(m); 3.00(s); 3.03(s); 3.19(t); 3.25(t); 3.42(m); 3.56-3.70(m); 6.80(m); 6.89-7.09(m); 7.15(d); 7.21(m); 7.30-7.50(m); 7.50-7.65 (m); 8.61(s); 8.63(s);

WO 02/20437

PCT/EP01/10419

11

8.64(s); 8.676(s); 10.73-10.83(m).

 $MS; m/z = 780 (MH^{+}).$

Example 8 - N.N.-bis-12-(1H-Indol-3-vI)-ethyll-N-methyl-N-I2-(4-phenylcarbamoyl-piperazin-1-vI)-ethyll-phthalamide

5 (R₄ = 2-(4-phenylcarbamoyl-piperazin-1-yl)-ethyl, and the other substituents as in Example 1)

1H-NMR; c.s.(ppm): 2.13(m); 2.18(m); 2.36(t); 2.45(m); 2.57(t); 2.77(s); 2.83(s); 2.90-3.03(m); 3.00(s); 3.03(s); 3.19(t); 3.25(t); 3.42(m); 3.56-3.70(m); 6.89-7.09(m); 7.15(d); 7.27(m); 7.27-7.48(m); 7.61(m); 8.41(s); 8.44(s);

10 8.46(s); 10.73-10.83(m).

 $MS; m/z = 696 (MH^*).$

Example 9 - N-[2-14-(3,4-dichloro-phenylcarbamoyl)-piperazin-1-yl)-ethyl)-N,N-bis-[2-(1H- indol-3-yl)-ethyl]-N-methyl-phthalamide $(R_4 = 2-[4-(3,4-dichloro-phenylcarbamoyl)-piperazin-1-yi]-ethyl, and the other substituents as In Example 1)$

substituents as in Example 1)
 1H-NMR; c.s.(ppm): 2.13(m); 2.18(m); 2.38(t); 2.42-2.47(m); 2.57(t); 2.77(s);
 2.83(s); 2.91-3.02(m); 2.99(s); 3.03(s); 3.19(m); 3.25(m); 3.39-3.45(m); 3.56-3.69(m); 6.80(m); 6.80-7.09(m); 7.15(d); 7.21(m); 7.27-7.48(m); 7.61(m); 7.82(m); 8.71-8.76(m); 10.73-10.83(m).

20 MS; m/z = 764 (MH⁺).

With a similar procedure the following compounds deriving from other appropriate symmetrical anhydrides were obtained:

Example 10 - c/s-but-2-enediolc acid b/s-f/2-(3,4-dichloro-phenyl)-ethyll-(3-morpholin-4-yl-propyl)-amide]

2s (A = c/s-but-2-ene, X = Y= CO, R₁= R₃= 2-(3,4-dichloro-phenyl)-ethyl, R₂= R₄ = 3-morpholin-4-yl-propyl)

1H-NMR; c.s.(ppm): 1.60(b,2H); 2.18(q); 2.22(t); 2.28(b); 2.76-2.85(m,2H); 3.18-3.25(m,2H); 3.47(m,2H); 3.54(b,4H); 6.33(s); 6.35(d); 6.49(d); 6.50(s); 7.23-7.27(m,1H); 7.50-7.57(m,2H).

 $MS; m/z = 713.5 (MH^*).$

8

Example 11 - naphthalene-2.3-dicarboxylic acid bis-fiz-(1H-indol-3-yl)-ethyll-(2. morpholin-4-yl-ethyl)-amidel

PCT/EP01/10419

82

(A = naphthalene 2,3 di-substituted , X = Y= CO, $R_1 = R_3 = 2-(1H-Indol-3-yl)$ -ethyl $R_2 = R_4 = 2$ -morpholin-4-yl-ethyl)

1H-NMR; c.s.(ppm); 2.10(b); 2.14(b); 2.40-2.48(m); 2.58(m); 3.03(b); 3.18(d); 3.24(t); 3.37-3.46(m); 3.54(t); 3.60(t); 3.70(t); 6.40(t); 6.71(m); 6.87-7.10(m); 7.24(m); 7.35(m); 7.60-7.68(m); 7.79(s); 7.88-7.94(m); 8.01(d); 10.72(b); 10.74(b); 10.84(b).

 $MS; m/z = 727 (MH^*).$

Example 12 - naphthalene-2.3-dicarboxylic acid bis-I[2-(5-fluoro-1H-indol-3-yl)-ethyl-3-morpholin-4-yl-propyl)-amide]

(R₁= R₃= 2-(5- fluoro-1H-indol-3-yl)-ethyl, R₂= R₄ = 3-morpholin-4-yl-propyl, and the other substituents as in Example 11)
 1H-NMR; c.s.(ppm): 1.93(b); 2.07(b); 2.88-3.88(m); 4.03(b); 6.55(d); 6.65(d); 6.76(m); 6.89-6.97(m); 7.08(s); 7.22-7.44(m);7.59-7.67(m); 7.74(s); 7.80-7.99(m); 9.63(b); 9.78(b);10.86(b); 10.91(b); 10.98(b); 11.01(b).

15 MS; m/z = 791 (MH*).

Example 13 - cyclohex-1-ene-1,2-dicarboxylic acid bis-fi2-(1H-Indol-3-yl)-ethyll-(2-morpholin-4-yl-ethyl)-amide]

(A = cyclohex-1-ene, X = Y= CO, R₁= R₃= 2-(1H-indol-3-yi)-ethyl, R₂= R₄ = 2-morpholin-4-yi-ethyl)

1H-NMR; c.s. (ppm): 1.84(b); 2.17(b); 2.22(b); 2.30-2.47(m); 2.84(q); 2.94(b); 3.43-3.56(m); 6.89(t); 6.94-7.15(m); 7.29-7.36(m,1H); 7.54(d); 7.58-7.65(m); 10.7-10.9(m,1H).

MS; $m/z = 681 \text{ (MH}^+)$.

Example 14 - pyrazin-2.3-dicarboxylic acid 2-f[2-(3.4-dichloro-phenyl)-ethyll-(3morpholin-4-y-propyl)-amidel 3-f[2-(1H-indol-3-yl)-ethyll-(3-morpholin-4-yl-propyl)amidel (A = pyrazin, X = Y = CO, $R_1 = 2 - (1H - Indol - 3 - yl) - ethyl, <math>R_2 = R_4 = 3 - Indol - 4 - yl - Indol - 2 - (3,4 - Ilchloro-phenyl) - ethyl)$

1H-NMR; c.s.(ppm): 2.01(b); 2.89-3.18(m); 3.24-3.72(m); 3.97(m); 6.86-7.13(m); 3.0 7.22(dd); 7.29-7.38(m); 7.43(dd); 7.52-7.65(m); 8.74(q); 8.78(d); 8.82-8.85(m); 9.67(b); 10.82(b); 10.85(b); 10.89(b).

MS; m/z = 736 (MH⁺).

WO 02/20437

PCT/EP01/10419

61

Example 15. pyrazin-2,3-dicarboxylic_acid_2-[12-(3,4-dichloro-phenyl)-ethyll-(3-morpholin-4-yl-propyl)-amide] 3-([2-(1H-Indo]-3-yl)-ethyll-amide}

 $(R_2 = H, and the other substituents are as described in the Example 14)$ 1H-NMR; c.s.(ppm): 1.55(m); 1.78(m); 2.00(m); 2.29-2.44(m); 2.74-2.82(m); 2.90-

3.04(m); 3.22-3.44(m); 3.52-3.70(m); 6.90-7.71(m); 8.74-8.87(m); 8.99-9.07(m); 10.80(s).

MS; $m/z = 609 \text{ (MH}^+\text{)}$.

With a similar procedure the following compounds deriving from asymmetriq anhydrides were obtained:

10 Example 16 - N',N²-bis-12-(1H-Indol-3-yl)-ethyll-N',N²-bis-(3-morpholin-4-yl-propyl)-4-nitro-phthatamide

(A = 4-nitro-benzene, X = Y= CO, R₁= R₃= 2-(1H-indol-3-yi)-ethyl, R₂= R₄ = 3-morpholin-4-yl-propyl))

1H-NMR; c.s.(ppm): 1.52-1.78(b); 2.09(m); 2.24-2.36(m); 2.93-3.71(m); 6.68-15 7.12(m); 7.18-7.36(m); 7.57-7.71(m); 7.86(m); 8.00(m); 8.13-8.34(m); 10.74-10.84(m).

 $MS; m/z = 750 (MH^{+}).$

Example 17 - naphthalene-1,2-dicarboxylic acid bis-[[2-(3,4-dichloro-phenyl)-ethyl)-(3-morpholin-4-yl-propyl)-amide]

20 (A = naphthalene 1,2 dl-substituted, X = Y= CO, R₁= R₃= 2-(3,4-dichloro-phenyl)-ethyl, R₂= R₄ = 3-morpholin-4-yl-propyl))

1H-NIMR; c.s.(ppm): 1.37(m); 1.51(m); 1.63-2.02(m); 2.33(m); 2.71-3.41(m); 3.59(m); 3.59(m); 3.68(m); 6.68(m); 6.91-6.97(m); 7.17(m); 7.23(m); 7.31-7.46(m); 7.53(m); 7.60(m); 7.60(m); 7.67(m); 7.53(m); 7.67(m); 7.67(m);

25 MS; m/z = 813 (MH*).

Example 18 - N', N²-bis-12-(1H-indol-3-vI)-ethyl N', N²-bis-12-morpholin-4-vI-ethyl)-4-nitro-phthalamide

 $(R_2=R_4=2\text{-morpholin-4-yl-ethyl},$ and the other substituents are as defined in Example 16)

30 1H-NMR; c.s.(ppm): 2.15(m); 2.35-2.4(m); 2.54(m); 2.74-3.24(m); 3.33-3.76(m); 6.68-7.41(m); 7.52-7.89(m); 8.15-8.34(m); 10.74-10.83(m).
MS; m/z = 722 (MH+*).

PCT/EP01/10419

20

Example 19 - N', N²-bis-l'2-(1H-Indot-3-vI)-ethyli-N', N²-bis-(3-mopholin-4-vIpropylt-3-nitro-phthalamide

(A = 3-nitro-benzene, and the other substituents are as defined in Example 16) 1H-NMR; c.s.(ppm): c.s.(ppm): 1.79-2.10(m); 2.75-4.03(m); 6.77-6.85(m); 6.92(m); 6.98-7.11(m); 7.18-7.38(m); 7.47(d); 7.55-7.69(m); 7.81-7.92(m); 8.29-8.39(m);

9.86(b); 10.78(b); 10.81(b); 10.83(b); 10.85(b); 10.90(b). MS; m/z = 750.5 (MH*). Example 20 - N'.N²-bis-12-(3,4-dichioro-phenyl)-ethyll-4-hydroxy-N'.N²-bis-(3morpholin-4-yl-propyl)-phthalamide (A = 4-hydroxy-benzene, X = Y= CO, R₁= R_3 = 2-(3,4-dichloro-phenyl)-ethyl, R_2 = R₄ = 3-morpholin-4-yl-propyl))

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1H-NMR; c.s.(ppm): 1.59-1.70(b); 2.10(b); 2.28(b); 2.33(b); 2.83(b); 3.10(b); 3.48-3.57(m); 6.58(b); 6.78(m); 6.97-7.10(m); 7.25-7.35(m); 7.48-7.57(m); 9.92(s). MS; m/z = 779 (MH*). 15 Example 21 - 4-Hvdroxy-N', N²-bis-12-(1H-Indol-3-vI)-ethvII-N', N²-bis-(3-morpholin-4-vI-propvI)-phthalamide

(A = 4-hydroxy-benzene, and the other substituents are as defined in Example 16) 1H-NMR; c.s.(ppm): 1.68(m,4H); 2.10(b); 2.24-2.37(m,6H); 2.92(m,4H); 3.17(m,2H); 3.38(b); 3.56(b,4H); 6.66(d); 6.75-6.86(m); 6.89(t); 6.84-7.19(m); 7.27-7.34(m,2H); 7.57(d); 7.62(t); 9.89(b); 9.94(b); 9.95(b); 10.74-10.81(m).

20 7.34(m,2H); 7.57(d); 7.62(t); 9.89(b); 9.94(b); 9.95(b); 10.74-10.81(m). MS; $mz = 721 \text{ (MH}^+)$.

Example 22 - N', N²-bis-12-(3.4-dichloro-phenyl)-ethylj-N', N²-bis-(3-morpholin-4-v)propyl)-4-nitro-phthalamide (A = 4-nitro-benzene, and the other substituents are as defined in Example 20)
14-NMR; c.s.(ppm): 1.98(b); 2.13(b); 2.74-2.94(m); 3.11-3.23(m); 3.33-3.61(m);
3.96(b); 6.81-6.88(m); 7.00(d); 7.06(m); 7.11(m); 7.21(d); 7.28-7.37(m); 7.40-7.45(m); 7.85(dd); 7.99(d); 8.17-8.27(m).

MS; m/z = 808 (MH⁺).

Example 23 - pyridin-3,4-dicarboxylic acid bis-li2-(3,4-dichloro-phenyl)-ethyl-13-

30 morpholin-4-yl-propyl)-amide]

(A = pyridin 3,4 di-substituted, and the other substituents are as defined in Example 20)

WO 02/20437

PCT/EP01/10419

7

1H-NMR; c.s.(ppm); 1.61-1.75(m,2H); 2.09(m); 2.26-2.35(m); 2.79-2.89(m); 3.02(m); 3.10(m); 3.49(m); 3.56-3.63(m); 7.02(m); 7.21(d); 7.28-7.39(m); 7.49-7.59(m); 8.42(b); 8.52(s); 8.55(s); 8.63(d); 8.67(m).

 $MS; m/z = 764 (MH^{+}).$

Example 24 - 4-amino-N', N²-bis-I2-(1H-indol-3-yl)-athyll-N', N²-bis-(3-morpholin-4-yl-propyl)-phthalamide

(A = 4-amine-benzene, and the other substituents are as defined in Example 16) 1H-NMR; c.s.(ppm): 1.97(b); 2.96-3.75(b); 3.96(b); 5.68(b); 6.45-6.66(m); 6.83-7.37(m); 7.62(b); 9.65(b); 10.79(b).

10 MS; m/z = 720.5 (MH*).

Example 25 - N°.N²-b/s-12-(1H-Indot-3-v))-ethyll-4-methanesulphonylamino-N°.N².

bis-(3-morpholin-4-yl-propyl)-phthalamide

(A = 4-methanesulphonylamino-benzene, and the other substtuents are as defined in Example 16)

1H-NMR; c.s.(ppm): 1.88(b); 2.00(b); 2.95(s); 3.00(s); 3.10(s); 3.14(s); 3.22-3.73(m); 3.92-4.01(m); 6.81-7.11(m); 7.18-7.40(m); 7.45(d); 7.61(m); 9.71(b); 10.15-10.28(m); 10.78-10.87(m).

 $MS; m/z = 798 (MH^*).$

Example 26 - toluene-4-sulphonic acid 3,4-bis-fi2-(1H-Indo-3-vI)-ethylH3-

20 morpholin-4-vi-propyl)-carbamovil-phenyl ester

(A = 4-tosylamine-benzene, and the other substituents are as defined in Example 16) 1H-NMR; c.s.(ppm); 1.53-1.75(m); 2.02-2.15(m); 2.18(s); 2.24(b); 2.25(s); 2.30(s); 2.34(s); 2.39(s); 2.82-2.98(m); 3.09(t); 3.16(t); 3.35-3.40(m); 3.54-3.63(m); 6.79-

25 7.48(m); 7.55(d); 7.60(t); 7.73(d); 7.80(d); 10.80(b).

 $MS; m/z = 875 (MH^{+}).$

Procedure B (from the chlorides of the acids)

82 mg of benzene disulphonyl chloride (0.30 mmol) were added to a mixture containing 0.33 mmol of amine B and 0.33 mmol of amine B1 and 9 ml of

dichloromethane, after addition of 3 ml of triethylamine. After sturing for a time ranging between 10 minutes and two hours at room temperature, the solvent and the excess of triethylamine were evaporated, and the crude product was divided

PCT/EP01/10419

22

between dichloromethane and a 10% aqueous solution of Na₂CO₃. The organic phase was washed once again with aqueous sodium carbonate, dried on anhydrous sodium sulphate, and filtered; the solvent was evaporated, and the product was purified by column chromatography and/or preparative HPLC.

In this way the following compounds were obtained:

Example 27 - benzene-1,2-disulphonic acid bis-fi2-(1H-i

14-NMR: c.s.(ppm): 1.65(qt,4H); 2.15-2.20(m,12H); 2.95(m,4H); 3.39(t,4H);
 3.47(t,8H); 3.56(m, 4H); 6.93(td,2H); 7.05(td,2H); 7.15(d,2H); 7.32(d,2H);
 7.44(d,2H); 7.78(m,2H); 8.01(m,2H); 10.83(d,2H).

 $MS; m/z = 777.5 (MH^*).$

Example 28 - benzene-1,2-disulphonic acid bis-[[2-(1H-Indol-3-vl)-ethyl]-(2-

22

(A = benzene, X = Y= SO₂ , R₁= R₃= 2-(1H-indol-3-yl)-ethyl, R₂= R₄ = 2-morpholin-4-yl-ethyl)

1H-NMR; c.s. (ppm): 2.31 (b, 4H); 2.44 (t, 2H); 2.98 (t, 2H); 3.47 (t, 4H); 3.52 (t, 2H); 3.57 (m, 2H); 6.93 (t, 1H); 7.04 (t, 1H); 7.14 (d, 1H); 7,32 (d, 1H); 7.45 (d, 1H); 7.76 (m, 1H); 8.08 (m, 1H); 10.82 (b, 1H).

20 7.45 (d, 1H); 7.76 (m, 1H); 8.08 MS; m/z = 749 (MH⁺). With a similar procedure the following compounds were obtained:

Example 29 - N.N. bis-12-(1H-indol-3-vI)-ethyl N.N. bis-13-mombolin-4-vI-propyl)-

phthalamide
25 (A = benzene, and the other substituents are as defined in Example 16)
1H-NMR; c.s.(ppm): 1.61-1.79(m,2H); 2.03-2.11(m,3H); 2.23-2.35(m,3H); 2.893.02(m,2H); 3.16(dt,1H); 3.33-3.39(m); 3.46(m,1H); 3.55-3.66(m,2H); 6.80(q);
6.89(t); 6.94-7.08(m); 7.18-7.39(m); 7.45(m); 7.56(d); 7.63(d).

30 Example 30 - N.N'-bis-f2-(3.4-dichloro-phenyl)-ethyl N.N'-bis-(3-morpholin-4-yl-propyl)-phthalamide

MS; $m/z = 705 (MH^{+})$.

(A = benzene, X = Y= CO, R₁= R₃= 2-(3,4-d)chloro-pheny)-ethyl, R₂= R₄ = 3-

WO 02/20437

PCT/EP01/10419

ឧ

morpholin-4-yl-propyl)

1H-NIMR; c.s.(ppm): 1.62(b,1H); 1.70(t,1H); 2.07(m,3H); 2.25-2.34(m,3H); 2.77-2.88(m,2H); 3.09(q,1H); 3.32(b); 3.49(t,1H); 3.57(m,2H); 6.98(td); 7.16(d); 7.25(dd); 7.29(m); 7.40-7.45(m); 7.49(dd); 7.53-7.59(m).

MS; $m/z = 763 (MH^+)$.

Example 31 - N-I2-(1H-indol-3-vI)-ethvII-N-methvI-N-(2-morpholin-4-vI-ethvI)-N-(2-naphhalene-2-vI-ethvI)-phthalamide

(A = benzene, X = Y= CO, R_1 = 2-(1H-indol-3-yl)-ethyl , R_2 = methyl, R_3 = 2 naphthalene-2-yl-ethyl, R_4 = 3-morpholin-4-yl-propyl)

14-NMR; c.s.(ppm); 2.11(b,1H); 2.16(b,1H); 2.33-2.53(m,4H); 2.77(s); 2.82(s);
 2.88-3.07(m); 3.00(s); 3.02(s); 3.16(t); 3.21(t); 3.37(t); 3.42-3.47(m); 3.52-3.58(m);
 3.62-3.73(m,2H); 6.78(m); 6.90(t); 6.94-7.08(m); 7.12(t); 7.21(s); 7.29(t); 7.32-7.54(m); 7.62(t); 7.73-7.89(m); 10.76(b); 10.77(b); 10.81(b); 10.82(b).

MS; m/z = 589 (MH*).

15 Example 32 - N.N-bis-f2-(3.4-dichloro-phenyl)-ethyll-N.N-bis-(2-morpholin-4-yl-ethyl)-phthelemide

 $(R_2=R_4=2\text{-morpholin-4-yi-ethyl},$ and the other substituents are as defined in Example 30)

1H-NMR; c.s.(ppm); 2.18(b,2H); 2.35-2.47(m,4H); 2.80-2.89(m,2H); 3.16(m,1H); 20 3.45-3.62(m); 6.97(t); 7.14(m); 7.27-7.35(m); 7.39-7.50(m); 7.55-7.60(m). MS; m/z = 735 (MH*).

Example 33 - N.N.-bis-12-(1H-indol-3-yl)-ethyll-N-methyl-N-(3-thiomorpholin-4-yl-

<u>propylbebithalamide</u> (A = benzene, X = Y= CO, R₁= R₃= 2-(1H-indol-3-yl)-ethyl , R₂= methyl, R₄ =3-

53

thlomorphollin-4-yl-propyl)
1H-NMR; c.s. (ppm): 1.55-1.75(m); 2.33(s); 2.36(s); 2.42(m); 2.52-2.64(m); 2.77(s); 2.83(s); 2.98(s); 3.01(s); 3.10(m); 3.16(m); 3.27-3.35(m); 3.45(b); 3.60-3.68(m); 6.77-6.82(m); 6.91(m); 6.95-7.08(m); 7.15-7.23(m); 7.26-7.38(m); 7.41-7.50(m); 7.56-7.64(m); 10.74-10.82(m).

30 MS; m/z = 608 (MH*).

Example 34 - N.N-b/s-12-(1H-Indot-3-y/)-ethyll-N.N-b/s-(3-th|omorpholin-4-y-propy/)-phthatamide

PCT/EP01/10419

74

(A = benzene, X = Y= CO, R₁= R₃= 2-(1H-Indol-3-yl)-ethyl , R₂= R₄ =3-thiomorpholin-4-yl-propyl)

1H-NMR; c.s.(ppm): 1.85(b); 2.02(b); 2.77-3.77(m); 6.77-7.11(m); 7.19(d); 7.22(m); 7.28-7.52(m); 7.60(d); 7.64(d); 9.49(b); 10.78(b); 10.81(b); 10.84(b); 10.87(b).

MS; $m/z = 737.5 \text{ (MH}^+\text{)}$.

Example 35 - N-(2-11,41bipiperidinyl-1'-vi-ethyl)-N.N-bis-12-(1H-indol-3-vI)-ethyll-N-methyl-phthalamide

(A = benzene, X = Y= CO, R₁= R₃= 2-(1H-*ind*ol-3-yl)-ethyl , R₂= methyl, R₄ =2-[1,4]Biplpendinyl-1-yl-ethyl)

2

1H-NMR; c.s.(ppm): 1.40(b); 1.68(b); 1.84(b); 2.12(b); 2.23(b); 2.31(b); 2.84(s); 2.87(s); 3.03(s); 3.06(s); 2.77-3.14(b); 3.27-3.87(b); 6.76-6.83(m); 6.91-7.17(m); 7.20-7.23(m); 7.29-7.66(m); 9.45(b); 10.78-10.88(m).

15 Example 36 - N.N.-bis.(3-11,41bipiperidinyL1'-vI-propyl)-N.N.-bis-12-(1H-indot-3-yl)-ethyl-phthalamide

MS; $m/z = 659 (MH^*)$.

(A = benzene, X = Y= CO, R₁= R₃= 2-(1H-Indol-3-yl)-ethyl , R₂= R₄ = 3- [1.4]Bipiperidinyl-1-yl-propyl)

1H-NMR; c.s.(ppm): 1.41(b); 1.62-2.05(m); 2.24(m); 2.73-3.70(m); 6.76-7.13(m); 20 7.18(d); 7.22(d); 7.30(dd); 7.34-7.52(m); 7.60(d); 7.66(d); 9.58-9.80(b); 10.78(bd); 10.82(d); 10.85(d); 10.92(d).

MS; m/z = 868. (MH*).

Example 37 - N.N-bis-(2-morpholin-4-vl-ethyl N.N-bis-(2-naphthalene-2-vl-ethyl)-phthalamide

25 (A = benzene, X = Y= CO, R₁= R₃= 2-naphthalene-2-yl-ethyl, R₂= R₄ = 2-morpholin-4-yl-ethyl)

1H-NMR; c.s.(ppm): 2.15(m,2H); 2.37-2.45(m); 2.53(q); 2.97-3.09(m,2H); 3.19(dt;1H); 3.37-3.47(m,3H); 3.55(m); 3.71(m,1H); 7.07-7.16(m,1H); 7.37(m,1H); 7.42-7.53(m); 7.73-7.89(m).

30 MS; m/z = 699 (MH*).

Example 38 - N.N-bis-12-(1H-Indol-3-vi)-ethyl N.N-bis-12-morpholin-4-vi-ethyl)-phthalamide

WO 02/20437

PCT/EP01/10419

 $\{A=benzene, X=Y=CO, R_1=R_3=2\cdot(1H-indol\cdot3-yl)-ethyl$, $R_2=R_4=2-morpholin-4-yl-ethyl$

23

1H-NMR; c.s.(ppm); 2.09-2.16(m); 2.34-2.44(m); 2.53(t); 2.91-3.02(m); 3.14-3.23(m); 3.33-3.58(m); 3.64(b); 3.69(b); 6.80(q); 6.90(t); 6.95-7.08(m); 7.22(m);

7.27-7.40(m); 7.46(m); 7.59(d); 7.64(d); 10.74(b); 10.76(b); 10.79(b); 10.81(b). MS; m/z = 677 (MH*).

Example 39 - N-[2-(1H-indol-3-vl)-ethyl]-N.N-bis-(2-morpholin-4-yl-ethyl)-N-42-naphthalene-2-yl-ethyl)-phthalemide

(A = benzene, X = Y= CO, R_t= 2-(1H-*ind*ol-3-yl)-ethyl , R₃= 2-naphthalene-2-ylethyl, R₂= R₄ =2-morpholin-4-yl-ethyl)

2

1H-NMR; c.s.(ppm): 2.14(t); 2.35-2.43(m); 2.54(m); 2.91-3.09(m); 3.14-3.23(m); 3.32-3.74(m); 6.76-7.54(m); 7.61(d); 7.84(d); 7.74-7.89(m); 10.74(b); 10.76(b); 10.82(b);

MS; m/z = 688 (MH*).

15 Example 40 - N.N-bis-12-(5-fluoro-1H-Indol-3-yl)-ethyrl-N.N-bis-(3-momholin-4-yl-propyl)-phthalamide

(A = benzene, X = Y= CO, R_i= R₃= 2-(5-Fluoro-1H-*ind*ol-3-y/)-ethyl , R₂= R₄ =3-morpholin-4-yl-propyl)

1H-NMR; c.s.(ppm): 1.88(b); 2.03(b); 2.96(b); 3.06-3.38(m); 3.43-3.80(m); 3.90-

20 4.02(m); 6.64(dd); 6.72(d); 6.82-6.95(m); 7.09(d); 7.11(d); 7.25-7.51(m); 9.77(b); 10.90(d); 10.92(d); 10.95(d); 10.99(d).

MS; m/z = 741 (MH*).

Example 41 - N.N-bls-12-(1H-Indok-3-yl)-ethyll-N-methyk-N-(3-morpholin-4-yk-propyl)-phthalamide

25 (A = benzene, X = Y= CO, R₁= R₃= 2-(1H-Indol-3-yI)-ethyI , R₂= methyI, R₄ =3-morpholIn-4-yI-propyI)

1H-NMR; c.s.(ppm): 1.58-1.78(m); 2.01-2.09(m); 2.25-2.35(m); 2.78(s); 2.83(s); 2.84-3.02(m); 2.98(s); 3.01(s); 3.13(t); 3.19(t); 3.27-3.41(m); 3.47(b); 3.57(m); 3.60-3.69(m); 6.79(m); 6.91(m); 6.95-7.09(m); 7.16(d); 7.20(d); 7.26-7.46(m);

30 7.61(m); 1074-10.82(m).

 $MS; m/z = 592 (MH^{+}).$

Example 42 - N.W-bis-(2-fbis-(2-methoxy-ethyl)-aminol-ethyl)-

PCT/EP01/10419

92

indol-3-vI)-ethyll-phthalamide

(A = benzene, X = Y= CO, R₁= R₃= 2-(1H-indol-3-yl)-ethyl , R₂= R₄ =2-[bls-(2-methoxy-ethyl)-amino]-ethyl)

1H-NMR; c.s.(ppm): 2.36-2.44(m); 2.56-2.74(m); 2.96(b); 3.10(s); 3.12(s); 3.09-3.18(m); 3.15(s); 3.22(s); 3.35(t); 3.40(t); 3.48(m); 3.62(b); 6.79(m); 6.88-7.08(m); 7.19-7.39(m); 7.44-7.51(m); 7.58(d); 7.64(d); 10.74(d); 10.76(d); 10.80(d); 10.81(d).

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 $MS; m/z = 769 (MH^*).$

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Example 43 - N-(2-(4-fN-(2-terf-butvl-phenyl)-carbamlmidovfl-piperazin-1-vfl-ethyl)-N.N-bis-12-(1H-Indot-3-vf)-ethyll-N-methyl-phthalamide

(A = benzene, X = Y= CO, R₁= R₃= 2-(1H-*Indo*I-3-yl)-ethyl , R₂= methyl, R₄ =2-(4-[N-(2-iert-butyl-phenyl)-carbamidoyl]-piperazin-1-yl)-ethyl) MS; m/z = 751(MH*).

Example 44 - N-(2-(4-IN-(2-ferf-butyl-phenyl)-N-methyl-carbamimidoyll-piperazin-15 1-yll-ethyl-N.N-bis-(2-(1H-indol-3-yll-ethyll-N-methyl-phthalamida

1-v/l-ethyl)-N.N-bis-[2-(1H-indol-3-v/l-ethyl]-N-methyl-phthalamide (R. =2-{4-[N-(2-tert-butyl-phenyl)- N-methyl -carbamidoyl]-piperazin-1-yl}-ethyl), and the other substituents as in Example 43)

MS; m/z = 765 (MH*).

Example 45 - N-(2-(4-1/4-(2-fert-butM-phenyl)-N-methyl-carbamlmidovII-piperazin-20 1-xII-ethyl)-N-42-(3.4-dichloro-phenyl)-ethyll-N42-(11H-indol-3-vl)-ethyll-N-methylphthalamide

(A = benzene, X = Y= CO, R₁= 2-(3,4-dichloro-phenyi)-ethyi, R₃= 2-(1H-Indol-3-yi)-ethyi , R₂= methyi, R₄ =2-(4-IN-(2-tert-butyl-phenyi)- N-methyi -carbamidoyil-piperazin-1-yi)-ethyi)

25 MS; m/z = 794 (MH*).

Example 46 - N-IZ-(3.4-dichloro-phenyl)-ethyll-N-IZ-(1H-Indot-3-vt)-ethyll-N-IZ-(4-phenylacetyl-piperazin-1-yl)-ethyll-phthalamide (R₁ = 2-(4-phenylacetyl-piperazin-1-yl)-ethyl, and the other substituents as in Example 45)

30 MS; m/z = 724 (MH*).

Example 47 - N.N-bis-12-(1H-indol-3-vI)-ethvil-N-methvi-N-12-14-(tricyclof3.3.1.1.0-0 decene-1-carbonyl)-piperazin-1-vil-ethyl)-phthelemide

WO 02/20437

PCT/EP01/10419

27

(A = benzene, X = Y= CO, R_1 = R_3 = $2\cdot(1H\cdot indol\cdot 3\cdot y)$ -ethyl , R_2 = H, R_4 = $\{2\cdot \{4\cdot (trcyclo[3.3.1.1^{0.0}]decane-1-carbonyl\}-piperazin-1-yl]-ethyl } said also <math>2\cdot \{4\cdot (adamantan-1-carbonyl)$ -piperazin-1-yl)-ethyl

MS; m/z = 739 (MH*).

Example 48 - N.N.-bis-12-(1H-Indol-3-vI)-ethvII-N-methyl-N-12-14-(tricyclol3,3.1.10-0]dec-1-vI-acetyl)-piperazin-1-vII-ethyl}-phthalamide

(R₄ = {2-[4-{tricyclo[3.3.1.1^{0,9}]dec-1-yl-acety}-piperazin-1-yl]-ethyl } said also 2-{4-(adamantan-1-yf-acetyl}-piperazin-1-yl}-ethyl, and the other substituents as in Example 47)

10 MS; m/z = 753 (MH⁺).

Example 49 - M-[2-(4-acetyl-piperazin-1-yl)-ethyll-N.N-bis-12-(1H-Indol-3-yl)-ethyll-N-methyl-phthalamide

(A = benzene, X = Y= CO, R₁= R₃= 2-(1H-Indol-3-yl)-ethyl , R₂= methyl, R₄ =2-(4-acetyl-piperazin-1-yl)-ethyl)

15 MS; m/z = 619 (MH*).

Example 50 - N.N-bis-12-(1.4-dloxa-8-aza-spiro[4.5]dec-8-vI)-ethvII-N.N-bis-12-

(1H-indot-3-vI)-ethvII-phthalamide

(A = benzene, X = Y= CO, R_1 = R_3 = 2-(1H-Indol-3-yl)-ethyl , R_2 = R_4 =2-(1,4-dioxa-8-aza-spiro[4.5]deo-8-yl)-ethyl)

 $MS; m/z = 789 (MH^*).$

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Example 51 - N-12-(1,4-dloxe-8-aza-spiro[4,5]dec-8-v/)-ethyll-N.N-bis-12-(1H-Indol-3-v/)-ethyll-N-methyl-phthalamide

 $(R_2=$ methyl, and the other substituents as in Example 50)

 $MS; m/z = 634 (MH^*).$

25 Example 52: N42-14-(Butane-1-sulfonyl)-piperazin-1-vil-ethyl)-N,N-bis-12-(1.H-indok-3-yl)-ethyl-N-methyl-phthalamide

(A = benzene, X = Y= CO, R₁= R₃= 2-(1*H*-Indol-3-yl)-ethyl, R₂= methyl, R₄ = 2-[4- (Butane-1-sutfonyl)-piperazin-1-yl]-ethyl

MS; m/z = 697 (MH+)

30 Example 53: N-[2-14-Allyloarbamoyl-piperazin-1-yl)-ethyll-N.N-bis-f2-(1/Hindol-3-yl)-ethyl-N-methyl-phthalamide

(R₄ = 2-(4-Allylcarbamoyl-piperazin-1-yl)-ethyl and the other substituents are as

PCT/EP01/10419

78

defined in Example 52)

MS; m/z = 660 (MH+)

Example 54; N.N-Bis-[2-[1H-Indol-3-vI)-ethvi]-N-methvi-N-[2-(4-thiomorpholin-4-vi-methyl-piperidin-1-vi)-ethvil-phthalamide

(R_4 = 2-(4-thlomorpholin-4-ylmethyl-piperidin-1-yl)-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 0.84-1.13(m); 1.31-1.81(m); 1.82-2.15(m); 2.26-2.60(m); 2.74-3.05(m); 3.31-3.39(m); 3.49-3.69(m); 6.71-7.79(m); 10.70-10.90(m).

MS; m/z = 691 (MH+)

10 Example 55: N.N.-Bis-[2-(1/H-indol-3-vl)-ethyfi-N-methyl-N-(2-(4-nltro-benzenesulfonyl-biperazin-1-vl]-ethyl-phthalamide

(R4 = 2-[4-(4-nitro-benzenesulfonyl)-piperazin-1-yl]-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 2.14-2.27(m); 2.32-2.43(m); 2.68(s); 2.75(s); 2.80(s); 2.77-15 (s); 2.93(s); 2.99(s); 3.06-3.16(m); 3.22-3.30(m); 3.55-3.68(m); 6.70-7.63(m); 7.90-8.03(m); 8.36-8.45(m); 10.70-10.90(m).

MS; m/z = 762 (MH+)

Example 56 MEN 14054: N.N-Bis-t2-(1H-Indot-3-xi)-ethyi]-N-methyi-N-f2-t4-phenyimethanesulfonyl-piperazin-1-yi)-ethyil-phthalamide

20 (R_4 = 2-(4-pheny/methanesulfonyl-piperazin-1-yl)-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 1.95-2.20(m); 2.30-2.57(m); 2.77(s); 2.82(s); 2.71-3.23(m); 3.33-3.72(m); 4.24-4.46(m); 6.73-7.69(m); 10.70-10.90(m).

MS; m/z = 731 (MH+)

2s Example 57: N.N-Bis-f2-(1H-Indol-3-yl)-ethyll-N-f2-(4-isopropyl-thiocarbamoyl-piperazin-1-yl)-ethyll-N-methyl-phthalamide

(R_4 = 2-(4-isopropylthiocarbamoyl-piperazin-1-yl)-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 1.08-1.15(m); 2.06-2.18(m); 2.33-2.59(m); 2.77(s); 2.82(s); 30 2.87-3.04(m); 2.99(s); 3.02(s); 3.16-3.47(m); 3.53-3.77(m); 4.45-4.56(m); 6.72-

7.66(m); 10.70-10.90(m). MS; m/z = 678 (MH+)

WO 02/20437

PCT/EP01/10419

53

Example 58: 3-(4-(2-([2-(H-Indol-3-v])-ethyl]-([2-([2-(H-Indol-3-v])-ethyl]-methyl-carbamoyl]-benzoyl]-aminol-ethyl]-piperazine-1-suffonyl}-thiophene-2-carboxylic acid methyl ester

(R_4 = 2-[4-(thlophene-2- (carboxylic add methyl ester) - 3-sulfonyl)-piperazin-1-yl]-

ethyl and the other substituents are as defined in Example 52)

MS; m/z = 781 (MH+)

Example 59: N.N-Bis-I2-(1H-Indol-3-yl)-ethyl]-N-methyl-N-(2-14-(thlophene-2-sulfonyl)-piperazin-1-yl-ethyl-phthalamide

($R_{\rm c}=2$ -[4-(thiophene-2-sulfonyl)-plperazin-1-yl]-ethyl and the other substituents

10 are as defined in Example 52)

MS; m/z = 723 (MH+)

Example 60 : N.N-Bis-[2-(1H-Indol-3-yl)-ethyll-N-methyl-N-42-14-(2-nitro-benzenesulfonyl)-piperazin-1-yll-ethyll-phthalamide

(R4 = 2-{4-(2-nitro-benzenesulfonyl}-piperazin-1-yl}-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 2.15-2.30(m); 2.33-2.57(m); 2.75(s); 2.81(s); 2.84-3.08(m); 2.94(s); 3.01(s); 3.10-3.20(m); 3.47-3.55(m); 3.59-3.89(m); 6.70-8.03(m); 10.70-10.90(m).

MS; m/z = 762 (MH+)

20 Example 61; NH2-I4-(Benzofblthiophene-2-carbonyl-piperazin-1-vfl-ethyll-N.Nbis-I2-(1H-indot-3-vl)-ethyll-N-methyl-phthelamide

($R_d \approx 2-[4-(Benzo[b])]$ thiophene-2-carbonyl)-piperazin-1-ylj-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 2.16-2.27(m); 2.38-2.62(m); 2.78(s); 2.83(s); 2.89-3.05(m); 2.99(s); 3.02(s); 3.15-3.44(m); 3.50-3.73(m); 6.73-8.11(m); 10.70-10.90(m).

MS; m/z = 737 (MH+)

Example 62: N-Y2-I4-(3,5-Dimethyl-Isoxazole-4-sulfonyl)-piperazin-1-vil-ethyl)-N.N-bis-Y2-(1H-indol-3-vi)-ethyl-N-methyl-phthalamide

(R₄ = 2-[4-(3,5-Dimethyl-Isoxazole-4-sulfonyl)-piperazin-1-ylj-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 2.22(s); 2.25-2.37(m); 2.42(s); 2.53-2.66(m); 2.78(s); 2.82(s); 2.55-3.05(m); 2.98(s); 3.01(s); 3.59-3.70(m); 6.71-7.68(m); 10.70-10.90(m).

WO 02/20437 PCT/EP01/10419

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MS; m/z = 736 (MH+)

Example 63: N-(2-14-IN-/2-tert-Butyl-phenyl)-N-furan-2-ylmethyl-carbamimidoyll-piperazin-1-vl}-ethyl-N.N-bis-[2-(1/H-indol-3-yl)-ethyl-N-methyl-phthalamide, acetic acid salt

(R₄ = 2-{4-[N-(2-fert-Butyl-phenyl)-N-furan-2-ylmethyl-carbamimidoyl]-piperazin-1-yl}-ethyl and the other substituents are as defined in Example 52)
1H-NMR; c.s.(ppm) 1.27-1.34(m);1.90(s); 2.07-2.19(m); 2.31-2.57(m); 2.77(s); 2.82(s); 2.85-3.08(m); 2.99(s); 3.02(s); 3.07-3.44(m); 3.50-3.72(m); 4.06-4.18(m); 5.29-5.49(br); 6.11-6.21(m); 6.30-6.40(m); 6.65-6.78(m); 10.70-10.80(m); 11.80-12.20(br,s).

MS; m/z = 831 (MH+)

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Example 64; N-22-43-IN-Furan-2-vimethyl-N-(2-methylsulfanyl-ethyl)-carbamimidoyil-piperazin-1-vi)-ethyl-N.N-bis-12-(1H-indol-3-vi)-ethyl-N-methyl-phthalamide, acetic acid salt

15 (R₄ = 2-{4-{N-Furan-2-ylmethyl-N-(2-methylsulfanyl-ethyl)-carbamimidoyll-piperazin-1-yl}-ethyl and the other substituents are as defined in Example 52)
1H-NMR; c.s.(ppm) 1.87(s); 1.97(s); 2.00(s), 2.02(s); 2.04(s);2.17-2.26(m); 2.37-2.67(m); 2.77(s); 2.82(s); 2.87-3.05(m); 2.98(s); 3.02(s); 3.12-3.34(m); 3.51-3.72(m); 4.25-4.41(m); 6.24-6.52(m); 6.72-7.81(m); 10.60-10.90(m)

MS; m/z = 773 (MH+)

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Example 65; N-(2-Benzolbithlophen-3-vi-ethyl)-N-[2-(4-benzyl-piperazin-1-vi)-ethyll-N-[2-(1 H-indol-3-vi)-ethyl-N-methyl-phthalamide

(A = benzene, X = Y= CO, R₁= 2-(1H-IndoH3-yl)-ethyl, R₂ = 2-(4-benzyl-piperazin-1-yl)-ethyl , R₃= methyl, R₄ = 2-Benzo[b]thlophen-3-yl-ethyl

25 1H-NMR; c.S.(ppm) 2.07-2.58(m); 2.77(s); 2.82(s); 2.86-3.01(m); 2.99(s); 3.02(s); 3.05-3.24(m); 3.27-3.42(m); 3.50-3.56(br); 3.61-3.75(m); 6.72-7.68(m); 7.88-8.03(m); 10.70-10.90(m).

MS; m/z = 684 (MH+)

8

Example 66: M-I2-(4-Benzyl-piperazin-1-vI)-ethyil-N-I2-(1*H*-indol-3-vI)-ethyil-N-methyl-N-I2-(4-nitro-phenyl)-ethyll-phthalamide

($R_4 = 2 - (4-n) \text{tro-phenyl}$ -ethyl and the other substituents are as defined in Example

WO 02/20437

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1H-NMR; c.s.(ppm) 2.04-2.54(m); 2.73(s); 2.77(s); 2.83-3.06(s); 2.93(s); 2.96(s); 3.11-3.19(m); 3.26-3.47(m); 3.49-3.57(m); 3.60-3.71(m); 6.73-6.81(m); 6.86-7.48(m); 7.54-7.65(m); 8.04-8.21(m); 10.70-10.90(m).

MS; m/z = 673 (MH+)

Example 67 MEN 14421: M-I2-(4-Benzyl-piperazin-1-yl)-ethyl)-N-/2-biphenyl-4-yl-ethyl)-N-I2-(11/Indol-3-yl)-ethyll-N/methyl-phthalamide (R4 = 2-biphenyl-4-yl-ethyl and the other substituents are as defined in Example

65)

1H-ŅMR; c.s.(ppm) 2.06-2.53(m); 2.76(s); 2.80(s); 2.78-2.98(m); 2.96(s); 2.99(s); 3.11-3.21(m); 3.23-3.46(m); 3.49-3.57(m); 3.58-3.70(m); 6.74-6.81(m); 6.89-7.67(m); 10.80-10.90(m).

MS; m/z = 704 (MH+)

PCT/EP01/10419

PCT/EP01/10419

32

| pKi | 9.1 | 8.6 | 8.0 | 7.7 | 7.8 | 8.4 | 8.0 | 8.1 | 8.2 | 8.3 | 8.5 | 8.5 | 9.0 | 8.6 | 8.7 | 8.3 | 9.2 | 8.7 |
|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Example | . 2 | 3 | 4 | 16 | 26 | ਲ | 42 | 50 | 52 | 55 | 56 | 57 | 58 | 29 | 09 | 61 | 62 | 65 |

The compounds that form the subject of the present invention have proven active on tachykinin receptors as antagonists or agonists, and their activity on these receptors has been evaluated by means of *in-vitro* preparations that are by now well known to the person skilled in the art.

In particular, the affinity of the compounds for the human NK2 receptor was evaluated in a binding test using Chinese hamster ovary (CHO) membranes transfected with the NK2 receptor of the human ileum and the radioligand (¹²⁵t)NKAn at the concentration of 100pM in competition studies, obtaining values of pKI of up to 9.2.

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The biological activity on the NK2 receptor was evaluated by means of *In-vitro* functional tests well known to the man skilled in the art, for example those

WO 02/20437

PCT/EP01/10419

performed on organs Isolated from gulnea pig (M. Tramontana et al. Eur. J. Pharmacol. 1998, 352, 279-288); P. Santicioli et al. Naunyn Schmieddeberg's Arch. Pharmacol. 1997, 35, 678-688) and/or functional tests on transfected huma cells (P.A. Iredale and J.M. Dickenson, Chapter 17 in "Signal Trasduction Protcols" D.A. Kendall and S.J. Hill eds. ISBN: 0-89603-298-1).

The activity demonstrated by the compounds of the present invention on tachykinin receptors means that they may potentially be used in numerous diseases in which tachykinins play a pathologically important role; these include: asthma, allergic rhinitis, chronic obstructive pulmonary disease, cough, urticaria,

inflammation (including that of a neurogenic origin), pain (including neuropathic, visceral and ocular pain), hemicrania, rheumatoid arthritis, pre-menstrual tension, emesis (including emesis resistant to ondensetron), oedema, gastric hypermotility, diseases due to oesophageal reflux, Crohn's disease, problems due to gastric evacuation, ulcerous collitis, the inflable-colon syndrome, hypermotility of the detrusor, uninary incontinence, cystitis, and renal colics.

In particular, the bronchospastic component of asthma, cough, pulmonary irritations, intestinal spasms (for exemple, in Crohn's disease, in ulcerous colitis or the irritable-colon syndrome), or local spasms of the bladder and of the ureter during cystitis, renal infections and colics can be considered conditions in which

20 the administration of NK2 antagonists may be effective.

WO 02/20437 PCT/RP01/10419

34

SMIN S

Compounds having the general formula (I)

5 in which the group:

is made up of:

a C_{2-12} alkenyl group or an aromatic group in which the two substituents X and Y

10 are bound to two adjacent carbon atoms;
X and Y, which are the same as or different from one another: represent

- X and Y, which are the same as or different from one another, represent a -CO-or else -SO₂- group;

- R₁ and R₃, which are the same as or different from one another, represent a -C₂, salkylidene-T-A₁ group in which T is a bond or a group chosen from among S, SO

or SO₂, and Ar₁ is an aromatic group chosen from among benzene, pyridine, pyrimldine, pyrazine, pyridazine, pyrrole, furan, thiophene, triazole, imidazole, oxazole, thiazole, isoxazole, naphthalene, quinoline, isoquinoline, quinazoline, quinoxaline, crinnoline, phthalazine, indole, IsoIndole, benzofuran, isobenzofuran, benzothlophene, isobenzothiophene, benzotrlazole, benzorazole, benzothlazole, benzotrazole, benzothlazole, benzoxazole, benzothlazole, benzoxazole, caroups chosen from among fluoro-, chloro-, bromo-, nitro-, cyano-, flydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethyk-, trifluoromethoxy-, amino-, methylamino-, dimethylamino-, acetyfamino-, mesylamino-, tosylamino-, tosylamino-, carboxy-, carboxy-, carboxy-, carboxy-, carboxy-,

25 - R₂ and R₄, which are the same as or different from one another, represent a group chosen from among H, -C_{1-s}alkyl, -C_{1-s}alkylidene-NR₅R₆ in which:
R₅ and R₆, which are the same as or different from one another, represent an H₁.

WO 02/20437

PCT/EP01/10419

35

C_{1-s}alkyl, -C_{2-s}alkylidene-Q group in which Q is a group chosen from between OR₇ and NR₇R₈, and in which R₇ and R₈, which are the same as or different from one another, represent an H, -C_{1-s}alkyl group; or NR₇R₈ together represent a group chosen from among piperidine, morpholine, pyrrolidine, thiomorpholine, thiomorpholine, thiomorpholin-1,-oxide, thiomorpholin-1,1-dioxide piperazine, N-methyl-piperazine, aziridine,

or else NRsRs together represent a group chosen from among:

a) pyrrolidine, morpholine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dloxide, guanidine, guanidine mono-substituted or di-substituted with -C₁₋₅alky/i or -C₁₋₅acyl, -NH-CH=NH,

-NH-C(R₁₂)=NH groups, where R₁₂ is a -C₁₋₆ alkyl group;

b) a 4-piperidon ethylene ketal group or else a piperidine of the type

in which R₀ is chosen from among H. -C_{1-s}alkyl, benzyl, OR₁₀. NR₁₀R₁₁, and in which R₁₀ and R₁₁, which are the same as or different from one another, represent an H, -C_{1-s}alkyl group, or else NR₁₀R₁₁ together represent a group chosen from among piperidine, morpholine, pyrrolldine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, piperazine, N-methyl-piperazine, and aziridine;

15

c) a piperazine of the type

In which E represents a bond or else a group chosen from among -CO-, -SO₂, ,-CONH-, -SO₂NH-, and R₁₃ Is a group chosen from among H, - C₁₋₃ alkyl, -(CH₂)_n-adamantyl, -(CH₂)_n- A₂, in which n = 0,1,2 and A₂ is an aromatic group chosen from between naphthalene and benzene possibly substituted with 1, 2, 3 groups

chosen from among F, Cl, CF₃, OH, OCH₃, SOCH₃, OCF₃, CN, C₁₋₅allxyl; with the limitation that at least one between R₂ and R₄ must always be a -C₁, salkylidene-NR₅R₆ group, as defined above;

25

the optical isomers, including those deriving from phenomena of atropolsomery, such as pure enantiomers or in racemic or non-racemic mixtures,

WO 02/20437 PCT/BP01/10419

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the pharmaceutically acceptable salts of these compounds with organic and inorganic acids chosen from the following group: hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, carbonic acid, acetic acid, trifluoroacetic acid, ulchloroacetic acid, oxalic acid, malonic acid, mailc acid, succinic acid, tartaric acid, citric acid, methanesulphonic acid, p-toluenesulphonic acid, maleic acid, and fumaric acid.

2. Compounds according to claim 1 in which the group:

5



is made up of:

10 a) an olefin chosen from between:

in which Z and W, which are the same as or different from one another, represent an H, $C_{1.6}$ alkyl group, or else together represent a $C_{2.6}$ alkylidene;

- b) an aromatic group Ar, either mono-cyclic or bl-cyclic, in which the substituents X and Y are in an ortho position with respect to one another and are chosen in the group made up of: benzene, pyridine, pyrimidine, pyriazine, pyridazine, pyrrole, furan, thlophene, triazole,
- imidazole, oxazole, thiazole, isoxazole, naphthalene, quinoline, fsoquinoline, quinoxaline, clinoline, phthalazine, indole, isoindole, benzofuran, lsobenzofuran, benzothlophene, isobenzothlophene, benzothlazole, benzothlazole, and benzolsoxazole,
- sald aromatic group being possibly further substituted with one, two, three or four groups, which are the same as or different from one another, chosen in the group made up of: fluoro-, chloro-, bromo-, nitro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, methylamino-, dimethylamino-, acetylamino-, tosylamino-, tosylamino-, tosylamino-, carboxy-, carboxyamido-, guanidino-, and sulphamido-;
- and the other substituents are as previously defined.

Compounds, according to claim 2, In which:

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WO 02/20437

PCT/EP01/10419

37

- R₁ and R₃, which are the same as or different from one another, represent a -C₂ salkylidene-T-Ar group in which T is a bond or a group chosen from between S and SO, and Ar₁ is an aromatic group chosen from among benzene, naphthalene, quinoline, isoquinoline, quinazoline, quinozaline, cinnoline, phthalazine, indole, isoindole, benzofuran, isobenzofuran, benzothlazole, and benzointophene, benzotriazole, benzolmidazole, benzoxazole, benzotriazole, and benzoisoxazole, possibly substituted with one or two groups chosen from among fluoro-, chloro-, cyano-, hydroxy-, methoxy-, methyt-, trifluoromethyt-, trifluoromethoxy-, amino-, acetylamino-, mesylamino-, tosylaxy-, guanidino-, and sulphamido-;

10 - R₂ and R₄, which are the same as or different from one another, represent a group chosen from among H, -C_{1.6}alkyl, -C_{1.6}alkylldene-NR₆R₆ in which:
R₅ and R₆, which are the same as or different from one another, represent an H,

-C_{1-s}alkyl, -C_{2-s}alkylidene-Q group in which Q is a group chosen from between OR, and NR₇R₈ and in which R₇ and R₈, which are the same as or different from one another, represent an H, -C_{1-s}alkyl group; or NR₇R₈ together represent a group chosen from among piperidine, morpholine, pyrrolldine, thlomorpholine, thlomorpholine, thlomorpholine, thlomorpholine, thlomorpholine, thlomorpholine 1-oxide, thlomorpholine 1,1-dloxide, piperazine, N-methyl-piperazine, or else NR₈R₈ together represent a group chosen from among:

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a) pyrrolidine, morpholine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-20 1,1-dioxide, guanidine, guanidine mono-substituted or di-substituted with -C1-e8lkyl

or -C₁₋₆acyl, -NH-CH=NH, -NH-C(R₁₂)=NH groups, where R₁₂ is a -C₁₋₆ alkyl group;

b) a 4-piperidon ethylene ketal group or else a piperidine of the type

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in which R₀ is chosen from among H, -C_{1.5}alkyl, benzyl, OR₁₀, NR₁₀R₁₁, and in which R₁₀ and R₁₁, which are the same as or different from one enother, represent an H, -C_{1.5}alkyl group, or else NR₁₀R₁₁, together represent a group chosen from among piperidine, morpholine, pyrrolidine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dloxide, piperazine, A-methyl-piperazine, and aziridine;

c) a piperazine of the type

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WO 02/20437 PCT/EP01/10419

38

In which E represents a bond or else a group chosen from among -CO-, -SO₂-, -CONH-, -SO₂NH-, and R₁₃ is a group chosen from among H, - C₁₋₃ alkyl, -(CH₂)_h-adamantyl, -(CH₂)_h- A₂, in which n = 0,1,2 and A₂ is an aromatic group chosen from between naphthalene and benzene possibly substituted with 1, 2, 3 groups chosen from among F, Cl, CF₃, OH, OCH₃, SOCH₃, OCF₃, CN, C₁₋₄alkyl;

with the limitation that at least one between R₂ and R₄ must always be a -C₁₋₅alkylidene-NR₅R₉ group, as defined above, and the other substituents are as defined above.

defined above.

10 4. Compounds according to claim 3, of the general formula (I) in which the group:



may be an olefin chosen from between



in which Z and W, which are the same as or different from one another, represent an H, C_{1.5} alkyl group, or else together represent a $C_{2\cdot6}$ alkylidene.

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5. Compounds according to claim 4, in which the -C_{2.6} alkylidene part of Z and W is chosen from among -(CH₂)s-, -(CH₂)s-, -(CH₂)s-, -(CH₂)s-, the -C_{2.6} alkylidene part of R, and R₃ part is chosen in the -(CH₂)r-, -(CH₂)r-, -(CH₂)r-, -(CH₂)r-, salkylidene part in R₂ and R₄ is chosen from among -CH₂r-, -(CH₂)r-, -(CH₂)r-, -(CH₂)r-, isopropylidene; -C_{1.6} alkyl is chosen from among methyl, ethyl, propyl, isopropyl, ter-butyl; and -C_{1.6} acyl is chosen from among formyl, acetyl, propanoyl, isopropanoyl.

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Compounds according to claim 5, in which Z and W, which are the same as or different from one another, are H or methyl or together represent a butylidene group, and X and Y represent a -CO- group.

7. The following compounds according to claim 6:

cis-but-2-enedloic acid bis-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-

WO 02/20437

PCT/EP01/10419

39

propyl)-amide];

- cyclohex-1-ene-1,2-dicarboxylic acid bis-[[2-(1H-Indol-3-yl)-ethyl]-(2-morpholin-4-yl-ethyl)-amide].

8. Compounds according to claim 3, in which the group:



Is an aromatic group Ar, either mono-cyclic or bi-cyclic, with the substituents X and Y in an ortho position with respect to one another,

chosen from among benzene, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, furan, thiophene, triazole, imidazole, oxazole, thiazole, isoxazole, naphthalene,

2

- quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, isolndole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, benzotriazole, benzotriazole, benzotriazole, benzotriazole, benzotriazole, possibly further substituted with one, two, three or four groups, which are the same as or different from one another, chosen from among fluoro-, chloro-, bromo-nitro- range.
 - nitro., cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, methylamino-, dimethylamino-, acetylamino-, mesylamino-, tosylamino-, tosylamino-, tosylaxioxy-, carboxy-, carboxyamido-, guanidino-, and sulphamido-.
 - 9. Compounds according to claim 8, in which:

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- the aromatic group Ar is chosen in the group made up of: benzene, pyridine, pyrazine, pyrimidine, naphthalene, quinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, benzofuran, benzothiophene, benzothlazole, and benzolsoxazole, and is possibly further substituted with one, two, three or four groups, which are the same as or different from one another chosen from among: fluoro-, chloro, nitro-, hydroxy-, methoxy-, methy-, trifluoromethyl-,
 - trifluoromethoxy, amino-, mesylamino-, and guanidino.

 10. Compounds according to claim 9 in which:

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- the aromatic group Ar is chosen in the group made up of benzene, naphthaiene, pyrazine, and pyridine, possibly further substituted with one, two, three or four groups, which are the same as or different from one another, chosen from among:
 - 30 fluoro-, chloro-, nitro-, amino-, hydroxy-, mesylamino-, and tosyloxy.
 - 11. Compounds according to claim 9 in which:

PCT/EP01/10419

4

R, and R₃, which are the same as or different from one another, represent a -C₂₋₅alkylidene-T-Ar₁ group In which T is a bond or a group chosen from between S and SO, and Ar₁ is an aromatic group chosen from among benzene, naphthalene, quinoline, indole, benzofuran, benzothlophene, benzoxazole, and benzothlazole, possibly substituted with one or two groups chosen from among fluoro-, chloro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, acetylamlino-, mesylamlino-, and guanidino.

12. Compounds according to claim 9 in which:

R₂ and R₄, which are the same as or different from one another, represent a group chosen from among H, -C₁₋₈alkyl, -C₁₋₈alkylidene-NR₅R₆, In which:

2

Rs and Rs, which are the same as or different from one another, represent an H, - C_{1-s}alkyl, -C_{2-s}alkylidene-Q group in which Q is an OR₇ group and in which R₇ represents an H, -C_{1-s}alkyl group, or else NR₅Rs together represent a group chosen from among:

15 a) pyrrolidine, morpholine, thlomorpholine, thlomorpholin-1-oxide, thlomorpholin-1,1-dioxide, guanidine, guanidine mono-substituted or di-substituted with "C₁₋₆alkyl or -C₁₋₆acyl, -NH-CH=NH, -NH-C(R₁₂)=NH groups , where R₁₂ is a -C₁₋₆ alkyl aron.

b) a 4-piperidone ethylene ketal group or else a piperidine of the type



in which R₈ Is chosen from among H, OH, pipendine, morpholine, thlomorpholine, thlomorpholin-1-oxide, thlomorpholin-1,1-dloxide;

c) a piperazine of the type

1s in which E represents a bond or else a group chosen from between -CO- and -CONH-, and R₁₃ is a group chosen from among H, - C_{1.6} alkyl, -(CH₂)_h-adamantyl, -(CH₂)_h- A_{7.6}, in which n = 0,1,2 and A_{7.2} is a benzene possibly substituted with 1, 2, 3 groups chosen from among F, Cl, CF₃, OH, OCH₃, SOCH₃, OCF₃, CN, and C_{1.6} alkyl.

WO 02/20437

PCT/EP01/10419

4

13. Compounds according to claims 9 to 12 in which:

the -C_{2-s}alkylidene part of R₁ and R₃ is chosen in the -(CH₂)₂-, -(CH₂)₄-, isopropylidene, and isobutylidene group; the -C_{1-s}alkylidene part in R₂ and R₄ is chosen from among -CH₂-, -(CH₂)₂-, -(CH₂)₄-, and isopropylidene;

-Ct-salkyl is chosen from among methyl, ethyl, propyl, isopropyl, butyl, ter-butyl; and -Ct-sacyl is chosen from among formyl, acetyl, propanoyl, and isopropanoyl.

14. The following compounds according to claims 10 to 13:

N.N-bis-{2-(1H-indol-3-yl)-ethyl]-N-methyl-N-{2-{4-(3-nitro-phenylcarbamoyl)-

piperazin-1-yl]-ethyl}-phthalamide

10 N-{2-[4-(2-tert-butyl-phenylcarbamoyl}-piperazin-1-yl]-ethyl}-N,N-bls-{2-(1H-Indol-3-yl)-ethyl]-N-methyl-phthalamide
N-[2-(4-benzyl-piperazin-1-yl)-ethyl]-N,N-bis-{2-(1H-indol-3-yl)-ethyl]-N-methyl-phthalamide

N-[2-(4-benzylcarbamoyi-plperazin-1-yl)-ethyl]-N.N-bis-[2-(1H-Indol-3-yl)-ethyl]-N-

methyl-phthalamide

2

M-[2-(4-benzyl-piperazin-1-yl)-ethyl]-N-[2-(1H-indol-3-yl)-ethyl]-N-(2-morpholin-4-yl-ethyl)-N-(2-naphthalene-2-yl-ethyl)-phthalamide

N-{3-(4-benzyl-piperazin-1-yl)-propyl]-N,N-b/s-{2-(1H-indol-3-yl)-ethyl]-N-methylnhthalamida

phthalamide

20 N,N-bís-{2-(1H-indok-3-yl)-ethylj-N-methyl-N-2-[4-(4-trifluoromethoxy-phenylcarbamoyl)-piperazin-1-ylj-ethyl}-phthalamide

N.N-bis-{2-{1H-Indol-3-yl}-ethyl]-N-methyl-N-[2-{4-phenylcarbamoyl-piperazin-1yl}-ethyl]-phthalamide

N-(2-[4-(3,4-dlchloro-phenylcarbamoyl)-piperazin-1-ylj-ethyl)-N,N-bis-(2-(1H-

25 Indol-3-yl)-ethyl]-N-methyl-phthalamide

c/s-but-2-enediolc acid bis-[[2-(3,4-djchloro-phenyl)-ethyl]-(3-morpholin-4-ylpropyl)-amide] Naphthalene-2,3-dicarboxylic acid b/s-[[2-(1H-Indol-3-y/)-ethyf]-(2-morpholin-4-y/-ethyl)-amide]

30 Naphthalene-2,3-dicarboxylic acid bis-[[2-(5-fluoro-1H-Indok-3-yl)-ethyl]-(3-morpholin-4-yt-propyl)-amide]

Cyclohex-1-ene-1,2-dicarboxylic acid bis-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholin-4-

WO 02/20437 PCT/EP01/10419

42

yl-ethyl)-amide]

Pyrazin-2,3-dicarboxylic acid 2-[[2-(3,4-dichloro-phenyl)-ethyl}-(3-morpholin-4-yl-propyl)-amide] 3-[[2-(1H-indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]
Pyrazin-2,3-dicarboxylic acid 2-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide] 3-[[2-(1H-indol-3-yl)-ethyl]-amide

N',N²-bis-{2-(1H-indol-3-yl}-ethyl]-N',N²-bis-{3-morpholin-4-yl-propyl}-4-nitro-

Naphthalene-1,2-dicarboxylic acid bis-[[2-{3,4-dichloro-phenyi}-ethyl]-(3-morpholin-4-yi-propyi)-amilde]

 N', N^2 -bis-{2-(1H-Indo-13-yi)-ethyl N', N^2 -bis-{2-morpholin-4-yi-ethyl}-4-nitro-phthalamide

2

//,//²*-bis-*{2-{1H-indol-3-yl}-ethyl]-*N',\/*²-*bis-*{3-morpholin-4-yl-propyl}-3-nltrophthalamide N', N^2 -bis-{2-(3,4-dichloro-phenyl)-elhyl]-4-hydroxy- N', N^2 -bis-(3-morpholin-4-yl-

propyl}-phthalamide 4-Hydroxy-*N¹,N²-bis-*[2-(1H-Indot-3-yl)-ethyl]-*N¹,N²-bis-*(3-morpholin-4-yl-propyl)-

phthalamide

~

N¹,N²-bis-[2-(3,4-dlchloro-phenyl}-ethyl]-N¹,N²-bis-(3-morpholin-4-yl-propyl)-4nitro-phthalamide 20 Pyridin-3,4-dicarboxylic acid bis-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]

4-amino-N', N²-bis-{2-(1H-indol-3-yl)-ethyl]-N', N²-bis-(3-morpholin-4-yl-propyl)-phthalamide

N¹,N²-bis-{2-{1H-indol-3-yl}-ethyl]-4-methanesulfonylamino-N¹,N²-bis-{3-morpholin-25 4-yl-propyl}-phthalamide Toluene-4-sulphonic acid 3,4-bis-[[2-(1H-indol-3-yl)-ethyl]-(3-morpholin-4-ylpropyl)-carbamoyl]-phenyl ester Benzene-1,2-disulphonic acid bis-[[2-(1H-Indol-3-yl)-ethyl]-(3-morpholin-4-ylpropyl)-amide]

30 Benzene-1,2-disulphonic acid bis-[[2-(1H-indot-3-yi)-ethyi]-(2-morpholin-4-yi-ethyi)amide]

N,N"-bis-{2-(1H-indol-3-yl)-ethyl N,N"-bis-(3-morpholin-4-yl-propyl)-phthalamide

WO 02/20437

PCT/EP01/10419

43

N,N'-bls-{2-(3,4-dichloro-phenyl)-ethyl N,N'-bis-{3-morpholin-4-yl-propyl}phthalamide

N-[2-(1H-*Ind*ol-3-yl)-ethyl]-N-methyl-N-(2-morpholin-4-yl-ethyl)-N-(2-naphthalene-2-yl-ethyl)-phthalamide

N,N-bis-[2-(3,4-dichloro-phenyl)-ethyl]-N,N-bis-(2-morpholin-4-yl-ethyl)-phthalamide
N,N-bis-[2-(1H-Indol-3-yl)-ethyl]-N-methyl-N-(3-thlomorpholin-4-yl-propyl)-

phthalamide N.N.-bis-{2-(1H-Indol-3-yl)-ethyl}-N.N-bis-(3-thiomorpholin-4-yl-propyl)-phthalamide[´]

10 N-{2-[1,4]Bipiperidinyl-1'-yl-ethyl}-N,N-bls-[2-{1H-indol-3-yl}-ethyl]-N-methyl-phthalamide

N,N-bis-(3-[1,4]bipiperidinyi-1'-yi-propyi)-N,N-bis-[2-(1H-Indoi-3-yi)-ethyi]phthalamide

printatamide N.N-*bis-*(2-morpholin-4-yl-ethyl N.N-*bis-*(2-naphthalane-2-yl-ethyl)-phthalamide 15 N,N-bis-[2-(1H-Indol-3-yl)-ethyl N,N-bis-(2-morpholln-4-yl-ethyl)-phthalamide N-[2-(1H-indol-3-yl)-ethyl]-N,N-bis-(2-morpholin-4-yl-ethyl)-N*-(2-naphthalene-2-yl-ethyl)-phthalamide

N.N-bis-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-N.N-bis-(3-morpholin-4-yl-propyl)-phthalamide

20 N.N-b/s-[2-(1H-indol-3-y/)-ethy/j-N-methyl-N-(3-morpholin-4-y/-propy/)-phthalamide

N,N-bis-{2-{bis-{2-methoxy-ethyl}-amino}-ethyl}- N,N-bis-{2-{1H-indol-3-yl}-ethyl}-phthalamide

N-(2-(4-[N-(2-tert-butyl-phenyl)-carbamimidoyi]-piperazin-1-yl)-ethyl)-N.N-bls-[2-23 (1H-Indot-3-yl)-ethyl]-N-methyl-phthalamide

N-(2-(4-[N-(2-4-1/N-Carbanimidoyi]-piperazin-1-yi]-ethyl)-N.N-bis-[2-(1H-indol-3-yi)-ethyl]-N-methyl-phthalamide

N-(2-{4-[N-(2-tert-buty/-phenyl)-N-methyl-carbamimidoyl]-piperazin-1-yl}-ethyl)-N-[2-(3,4-dichloro-phenyl)-ethyl]-N-[2-(1H-indol-3-yl)-ethyl]-N-methyl-phthalamide N-12-(3,4-dichloro-phenyl)-ethyll_N-12-(1H-indol-3-yl)-ethyll_N-roethyll N-12-(1

30 N-[2-(3,4-dichloro-phenyl)-ethyl]-N-[2-(1H-indol-3-yl)-ethyl]-N-methyl-N-[2-(4-phenylace)t/-piperezin-1-yl)-ethyl]-pithalamide N/N-bis-[2-(1H-indol-3-yl)-ethyl]-N-methyl-N-(2-[4-(trlcyclo[3.3.1.1^{0,0}]decane-1-

PCT/EP01/10419

4

carbonyl}-piperazin-1-yl]-ethyl}-phthalamide

N,N-bis-{2-(1H-indol-3-yl)-ethyl}-N-methyl-N-{2-[4-(tricyclo[3.3.1.1^{0,0}]dec-1-ylасеtyl)-piperazin-1-yl]-ethyl}-phthalamide N-{2-(4-acetyl-piperazin-1-yl)-ethylj-N,N-bis-{2-(1H-indol-3-yl)-ethylj-N-methyl-

phthalamide N,N-bis-{2-(1,4-dloxa-8-aza-spiro[4,5]dec-8-yl}-ethyl]-N,N-bis-{2-(1H-Indol-3-yl)ethyl}-phthalamide N-[2-(1,4-dioxa-8-aza-spiro[4,5]dec-8-yl)-ethylj-N,N-bls-|2-(1H-Indol-3-yl)-ethylj-Nmethyl-phthalamide

10 N4(2-[4-(Butane-1-sulfonyl)-piperazin-1-yl]-ethyl)-N,N-bis-(2-(1H-indol-3-yl)-ethyl]-N-methyl-phthalamide

N-[2-(4-Allylcarbamoyl-piperazin-1-yi)-ethyi]-N,N-bis-[2-(1*H*-indok-3-yi)-ethyf]-Nmethyl-phthalamide

N,N-Bis-[2-(1*H-*Indol-3-yl)-ethyl]-N-methyl-N-[2-(4-thlomorpholin-4-yl-methyl-

15 piperidin-1-yl)-ethyl]-phthalamide

N,N-Bis-[2-(1H-indol-3-yl)-ethyl]-N-methyl-N-(2-[4-(4-nitro-benzenesulfonyl)piperazin-1-yi]-ethyl}-phthalamide

N,N-Bis-[2-(1*H*-Indol-3-yl)-ethylj-N-methyl-N-[2-(4-phenylmethanesulfonylpiperazin-1-yl)-ethylj-phthalamide 20 N,N-Bis-[2-(1H-indol-3-yl)-ethyl]-N-[2-(4-isopropyl-thiocarbamoyl-piperazin-1-yl)-ethyl]-N-methyl-phthalamide

3-{4-{2-[[2-(H-Indol-3-yi)-ethyi]-(2-{[2-(H-indol-3-yi)-ethyi]-methyl-carbamoyi}-benzoyi)-amino]-ethyi]-piperazine-1-sulfonyi)-thiophene-2-carboxyiic acid methylester

25 N,N-Bis-{2-(1H-Indol-3-yl)-ethyl]-N-methyl-N-{2-{4-(thlophene-2-sulfonyl)-piperazin-1-yl]-ethyl}-pthalamide

N,N-Bis-{2-(1H-Indol-3-yl)-ethyl]-N-methyl-N-{2-{4-(2-nitro-benzenesulfonyl)-

piperazin-1-yl]-ethyl}-phthalamide

N-{2-[4-(Benzo[b]thiophene-2-carbonyl)-piperazin-1-yl]-ethyl}-N,N-bls-[2-(1H-Indol-3-yl)-ethyl]-N-methyl-phthalamide

N-{2-[4-(3,5-Dimethyl-Isoxazole-4-sulfonyl)-piperazin-1-yl]-ethyl}-N,N-bls-{2-(1*H*-indol-3-yl)-ethyl]-N,-methyl-phthalamlde

9

WO 02/20437

PCT/EP01/10419

45

N-(2-(4-I_N-(2-tert-Butyl-phenyl)-N-furan-2-ylmethyl-carbamimidoyl]-piperazin-1-yl}-ethyl)-N,N-bis-[2-(1*H*-indol-3-yl)-ethyl]-N-methyl-phthalamide, acetic acid salt N-(2-(4-IN-Furan-2-ylmethyl-N-(2-methylsulfanyl-ethyl)-carbamimidoyl]-piperazin-

1-yl)-ethyl)-N,N-bis-[2-(1H-indol-3-yl)-ethyl]-N-methyl-phthalamide, acetic acid salt N-(2-Benzo[b]thlophen-3-yl-ethyl]-N-[2-(4-benzyl-piperazin-1-yl)-ethyl]-N-[2-(1H-indol-3-yl)-ethyl]-N-methyl-phthalamide

N-[2-(4-Benzyl-piperazin-1-yl)-eithyl]-N-[2-(1*H*-indol-3-yl)-eithylj-N-meithyl-N-[2-(4nitro-phenyl)-eithylj-phthalamide N-[2-(4-Benzyl-piperazin-1-yl)-ethyi]-N-(2-biphenyl-4-yl-ethyl)-N-[2-(1H-indok-3-yl)-

10 ethyl]-N-methyl-phthalamide

15. Pharmaceutical compositions containing as active principle compounds according to any one of claims from 1 to 14.

16. Use of compounds according to any one of claims 1 to 14 for the preparation of pharmaceutical compositions suitable for the treatment of diseases in which

15 fachykinin receptors are implicated.

17. Use of compounds according to claim 16 for the preparation of pharmaceutical compositions suitable for the treatment of diseases in which the use of tachykinin antagonists is indicated.

Use of compounds according to claim 17 for the preparation of pharmaceutical
 compositions suitable for the treatment of diseases in which the use of NKZ antagonists is indicated.

19. Use of compounds according to claim 18 for the preparation of pharmaceutical compositions suitable for the treatment of the bronchospastic component of asthma, cough, pulmonary Irritations, intestinal spasms in general, Crohn's

disease, ulcerous colitis, the irritable-colon syndrome, local spasms of the bladder and of the ureter during cystitis, and renal infections and colics.